

Correlation of QRS/T angle with clinical, echocardiographic, and hemodynamic variables in chronic thromboembolic pulmonary hypertension patients

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ABSTRACT

Objectives: In this study, we aimed to examine the relationships between frontal QRS-T (fQRS-T) angle prognostic risk factors outlined in the current pulmonary hypertension (PH) guidelines and to demonstrate whether the fQRS-T could detect patients with unfavorable echocardiographic and hemodynamic data.

Patients and methods: Between July 2009 and February 2023, a total of 33 patients (8 males, 25 females; median age: 61 years; range, 55 to 70 years) with chronic thromboembolic pulmonary hypertension (CTEPH) who underwent electrocardiographic (ECG) examination were retrospectively analyzed. The fQRS-T angle was calculated from surface ECGs. Functional class, 6-min walk distance, and brain natriuretic peptide values were recorded. Two-dimensional echocardiographic data including comprehensive right ventricular (RV) functions, right atrial area (RAA), tricuspid annular systolic plane excursion (TAPSE), systolic pulmonary artery pressure (sPAP), and TAPSE/sPAP ratio were noted. Among invasive hemodynamic variables, sPAP, mean PAP (mPAP), pulmonary vascular resistance (PVR), and cardiac index (CI) were obtained. The correlations between clinical, echocardiographic, and hemodynamic variables were analyzed.

Results: There was no significant correlation between clinical variables and fQRS-T angle. The TAPSE and TAPSE/sPAP ratio were negatively correlated with fQRS/T angle ($r=-0.37$, $p=0.02$, $r=-0.35$, and $p=0.03$, respectively), whereas RV Tei index and RAA were positively correlated with the fQRS-T angle ($r=0.53$, $p=0.014$, $r=0.47$, and $p=0.007$, respectively). The hemodynamic data including sPAP, mPAP, and PVR were positively correlated with the fQRS-T angle ($r=0.32$, $p=0.048$, $r=0.34$, $p=0.034$, $r=0.35$, and $p=0.02$, respectively) and CI was negatively correlated with the fQRS-T angle ($r=-0.30$, $p=0.048$).

Conclusion: Our study results suggest that the fQRS/T angle is correlated with poor prognostic echocardiographic and hemodynamic variables in CTEPH patients.

Keywords: Chronic thromboembolic pulmonary hypertension, electrocardiography, QRS-T angle.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a possible mortal late consequence of acute pulmonary embolism promoted by ongoing occlusion of the pulmonary arteries (PAs) by organized thrombus, resulting in flow dispersion and alterations in the pulmonary microvasculature. It is the fibrotic transformation of the PA thrombus, which causes constant mechanical obstruction in the PAs and an increase in the flow in the open PA bed.^[1] Chronic thromboembolic pulmonary hypertension is an underrecognized and is one of the potentially mortal groups of pulmonary hypertension (PH), if left untreated.^[2] The gold-standard treatment of choice in CTEPH patients is pulmonary endarterectomy, which significantly improves invasive hemodynamics.^[3]

Various clinical, echocardiographic, and hemodynamic variables are currently used in risk stratification in Group 1 PH.^[4] It has been demonstrated that European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification tool is also appropriate in CTEPH

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patients.^[5] Nevertheless, additional more simplified risk assessment tools are warranted in patients with PH.

Electrocardiography (ECG) is a basic, readily accessible diagnostic modality in patients with cardiovascular disease and can mirror the cardiac anatomical and hemodynamic changes induced by PH in terms of cardiac electrical activity in CTEPH patients.

The frontal QRS-T (fQRS-T) angle is expressed as a manifestation of myocardial repolarization and depolarization diversity and is computed by the difference between ventricular depolarization (QRS axis in ECG) and repolarization (T wave).^[6] It has been shown that alterations in QRS-T angle correlate with echocardiographic systolic PA pressure (sPAP), right atrial (RA) and right ventricular (RV) size, and impaired RV functions in CTEPH patients.^[7]

In the present study, we aimed to examine the relationships between fQRS-T angle prognostic risk factors outlined in the current PH guidelines and to demonstrate whether the fQRS-T could detect patients with unfavorable echocardiographic and hemodynamic data.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Dokuz Eylül University Faculty of Medicine, Department of Cardiology between July 2009 and February 2023. Initially, a total of 81 patients with CTEPH were screened. The diagnosis of CTEPH was made based on an invasively measured mean PA pressure (mPAP) of higher than 25 mmHg and a pulmonary capillary wedge pressure (PCWP) of less than 15 mmHg and perfusion defects as assessed by conventional pulmonary angiography, computed tomography pulmonary angiography and ventilation-perfusion scintigraphy after at least three months of optimal anticoagulation treatment. Electrocardiographic readings were obtained from 43 patients. The ECGs were recorded at the first diagnostic workup of PH patients before echocardiographic examination or right heart catheterization (RHC). Inclusion criteria were age between 18 and 90 years and having a diagnosis of CTEPH. Exclusion criteria were as follows: age <18 or >90 years, having bundle branch block, atrioventricular block, permanent pacemaker,

ineligible or missing ECG readings, severe liver failure or chronic renal failure, and active malignancy. Finally, a total of 33 patients (8 males, 25 females; median age: 61 years; range, 55 to 70 years) who met the inclusion criteria were recruited.

Data collection

Institutional medical records were used for demographic, anthropometric, laboratory, ECG, echocardiographic, and hemodynamic data. The laboratory parameters including baseline serum glucose, creatinine, estimated glomerular filtration rate (eGFR), and brain natriuretic peptide (BNP) were recorded.

Electrocardiography

Utilizing a paper rate of 25 mm/sec and a standard deviation of 0.1 mV/mm, a 12-lead ECG was obtained from each patient. Heart rate (HR), PR interval, QRS duration, QT and QTc interval, QRS axis, and T axis were all automatically computed by the ECG machine and examined by a cardiologist. Using the T and QRS axis, the fQRS-T angle was computed. If the computed angle was more than 180 degrees, $360 - [\text{obtained angle}]$ was determined as the fQRS-T angle (Figure 1).

Echocardiography

A Philips HD 11 XE ultrasound system (Philips, Andover, MA, USA) with a 3.2 MHz transducer was used for echocardiographic examination. The RV-focused apical four-chamber (4C) view was used for the linear longitudinal end-diastolic dimension of RV (RVd). The RV fractional area change (RVFAC) was computed as $(\text{area at end of diastole} - \text{area at the end of systole}) / \text{area at end of diastole} \times 100\%$.^[8] In the apical 4C view, an M-mode cursor was set along the lateral RV wall to the tricuspid annulus. The maximum length of tricuspid annulus movement along systole was specified as tricuspid annular systolic plane excursion (TAPSE). The RA area (RAA) was calculated at the end of the systole from the apical 4C view.

Tissue Doppler imaging was utilized to record the RV systolic (RV S') rate and RV Tei index. The RV Tei index was determined by dividing the ejection period by the summation of the contraction duration and isovolumetric relaxation duration.^[8] Continuous-wave Doppler was used for recording tricuspid regurgitation velocity (TRV). The peak TR gradient was computed by the modified Bernoulli equation $[4 \times \text{TRV}^2]$. The inferior vena cava (IVC) was visualized from

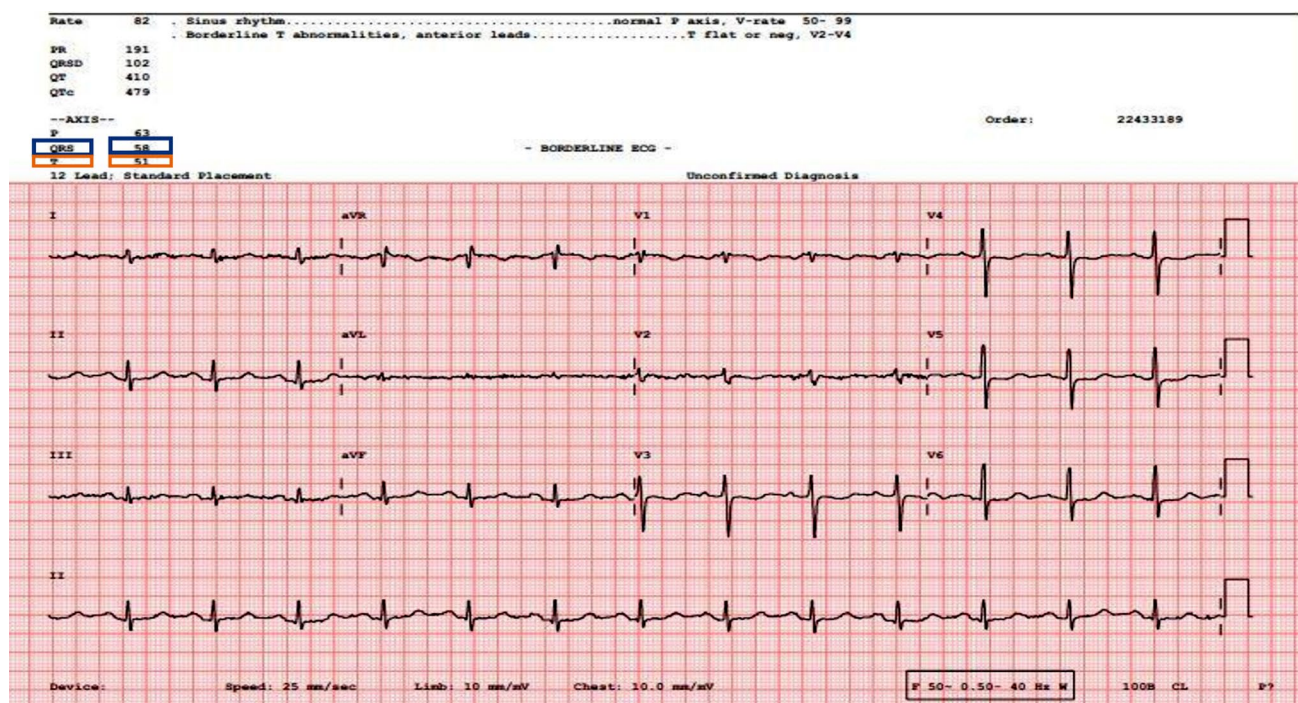


Figure 1. An ECG example showing the measurement of the QRS-T angle. The QRS axis and T axis were all automatically computed by the ECG (arrowheads). Using the T and QRS axis, the fQRS-T angle was computed. If the computed angle was more than 180 degrees, 360 - [obtained angle] was determined as the fQRS-T angle. For this ECG example, the QRS-T angle is 7° (QRS angle= 58°, T angle= 51°).

ECG: Electrocardiographic; fQRS-T: Frontal fQRS-T.

Table 1					
Baseline characteristics of patients					
Variables	n	%	Mean±SD	Median	IQR
Age (year)				61	55-70
Sex					
Female	25	75.8			
Body mass index (kg/m ²)			28.8±7.4		
6-minute walk distance (m)				320	120-400
Brain natriuretic peptide (pg/mL)		220	83-450		
Serum glucose (mg/dL)				101	87.5-120.5
Creatinine (mg/dL)				0.8	0.7-1.05
eGFR (mL/min/1.73 m ²)			76.9±25.5		
NYHA functional class					
Class II	9	27.3			
Class III	22	66.7			
Class IV	2	6			
Medications					
Bosentan	2	6			
Macitentan	1	3			
Epoprostenol	1	3			
Treprostinil	1	3			
Riociguat	24	72.7			

SD: Standard deviation; IQR: Interquartile range; eGFR: Estimated glomerular filtration rate; NYHA: New York Heart Association.

the subcostal view, and patients were advised to quickly inhale or “sniff” throughout the procedure. The RA pressure was estimated using the inspiratory magnitude of IVC collapse and the size of the IVC.^[9] The sum of RA pressure and anticipated peak TR gradient was recorded as sPAP.

Right heart catheterization

An expert cardiologist conducted RHC using femoral access, while the patient was at rest and without anesthesia. The RA pressure, PCWP, mPAP, diastolic, and systolic PA pressures (dPAP, and sPAP,

Table 2 Electrocardiographic, echocardiographic, and hemodynamic data of the patients (n=33)					
	n	%	Mean±SD	Median	IQR
Electrocardiographic data					
Heart rate (bpm)			84±14		
PR interval (msec)			153±38		
QRS duration (msec)				90	87-93
QT interval (msec)			387±36		
QTc (msec)				447	437-464
Frontal QRS-T angle°				47	20-93.5
Echocardiographic data					
RV diameter (mm)			36±7.6		
RV FAC (%)			23.8±8.9		
TAPSE (mm)			17.6±5.4		
RV S' (cm/s)			10.7±3.9		
RV Tei index (%)			46.7±25.9		
Right atrial area (cm ²)			22.1±3.9		
sPAP (mmHg)			70.6±28.1		
TAPSE/sPAP (mm/mmHg)				0.25	0.14-0.39
Tricuspid regurgitation	11	33.3			
Mild	8	24.2			
Moderate	14	42.3			
Severe	3	9.1			
Pericardial effusion					
Hemodynamic data					
sPAP (mmHg)			75.6±24.7		
mPAP (mmHg)			42±12.7		
dPAP (mmHg)				27.5	21.7-31.5
PCWP (mmHg)			12.9±4		
PVR (Woods)			10.3±7.5		
CO (L/min)			3.7±0.9		
CI (L/min/m ²)			2.1±0.6		
RA pressure (mmHg)			11.9±6.9		
MVO ² (%)			57.8±8.3		
SD: Standard deviation; IQR: Interquartile range; RV: Right ventricle; S': Systolic velocity; FAC: Fractional area change; TAPSE: Tricuspid annular plane systolic excursion; sPAP: Systolic pulmonary artery pressure; mPAP: Mean pulmonary artery pressure; dPAP: Diastolic pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; CO: Cardiac output; CI: Cardiac index; RA: Right atrium; MVO ² : Mixed venous oxygen saturation.					

respectively) were recorded. Blood gas analyses were obtained. The indirect Fick method was used to evaluate cardiac output (CO). Cardiac index (CI) was calculated as CO/body surface area and the pulmonary vascular resistance (PVR) was determined as [mPAP-PCWP]/CO.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). The normality of the continuous data was checked with histograms and the Kolmogorov-Smirnov test. Continuous data were expressed in mean \pm standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. The Pearson and Spearman correlation analyses were used to identify the associations between the fQRS-T angle and clinical, laboratory, echocardiographic, and hemodynamic variables. A *p* value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the patients are shown in Table 1. Twenty-two (66.7%) patients had New York Heart Association Class III symptoms and 24 (72.7%) patients received riociguat treatment. The median 6-min walk distance was 320 (range, 120 to 400) m and the median BNP was 220 (range, 83 to 450) pg/mL.

Electrocardiographic, echocardiographic, and hemodynamic data of the patients are presented in Table 2. The mean HR was 84 ± 14 bpm and the median fQRS-T angle was 47° (range, 20 to 93.5°) degrees. The mean echocardiographic RAA was 22.1 ± 3.9 cm² and the median TAPSE/sPAP ratio was 0.25 (range, 0.14 to 0.39) mm/mmHg. Only three patients (9.1%) had pericardial effusion. The RHC data revealed that the mean RA pressure was 11.9 ± 6.9 mmHg, the mean CI was 2.1 ± 0.6 L/min/m², and the mean mixed venous oxygen saturation was $57.8 \pm 8.3\%$.

The correlations between the fQRS-T angle and clinical, laboratory, echocardiographic, and hemodynamic variables are given in Table 3 and Figure 2. Accordingly, there was no significant correlation between the fQRS-T angle and clinical and laboratory characteristics of the patients. Among echocardiographic data, however, TAPSE and TAPSE/sPAP ratio were negatively correlated

Table 3
The bivariate correlations between the fQRS-T angle and clinical, laboratory, echocardiographic, and hemodynamic parameters

	Frontal QRS-T angle	
	r	p
Clinical and laboratory parameters		
NHYA functional class	0.29	0.1
Six-minute walk distance (m)	-0.23	0.2
Brain natriuretic peptide (pg/mL)	0.06	0.7
Echocardiographic parameters		
RV diameter (mm)	0.17	0.29
RV FAC (%)	-0.24	0.24
TAPSE (mm)	-0.37	0.02
RV S' (cm/s)	-0.06	0.72
RV Tei index (%)	0.53	0.014
Right atrial area (mm ²)	0.47	0.007
sPAP (mmHg)	0.26	0.09
TAPSE/sPAP	-0.35	0.03
Hemodynamic parameters		
sPAP (mmHg)	0.32	0.048
mPAP (mmHg)	0.34	0.034
dPAP (mmHg)	0.14	0.41
PCWP (mmHg)	-0.09	0.58
PVR (Woods)	0.35	0.02
CO (L/min)	-0.29	0.07
CI (L/min/m ²)	-0.30	0.048
RA pressure (mmHg)	0.23	0.15
MVO ² (%)	-0.15	0.4

fQRS-T: Frontal QRS-T; NHYA: New York Heart Association; RV: Right ventricle; FAC: Fractional area change; TAPSE: Tricuspid annular plane systolic excursion; S': Systolic velocity; sPAP: Systolic pulmonary artery pressure; mPAP: Mean pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; CO: Cardiac output; CI: Cardiac index; RA: Right atrium; MVO²: Mixed venous oxygen saturation.

with fQRS/T angle ($r=-0.37$, $p=0.02$, and $r=-0.35$, $p=0.03$, respectively), whereas the RV Tei index and RAA were positively correlated with fQRS-T angle ($r=0.53$, $p=0.014$, and $r=0.47$, $p=0.007$, respectively). The hemodynamic data including sPAP, mPAP, and PVR were positively correlated with fQRS-T angle ($r=0.32$, $p=0.048$, $r=0.34$, $p=0.034$, and $r=0.35$, $p=0.02$, respectively) and CI was negatively correlated with the fQRS-T angle ($r=-0.30$, $p=0.048$).

DISCUSSION

The present study is a rare report in the current literature to highlight the importance of the fQRS-T angle, which is an ECG sign of myocardial repolarization and depolarization heterogeneity,

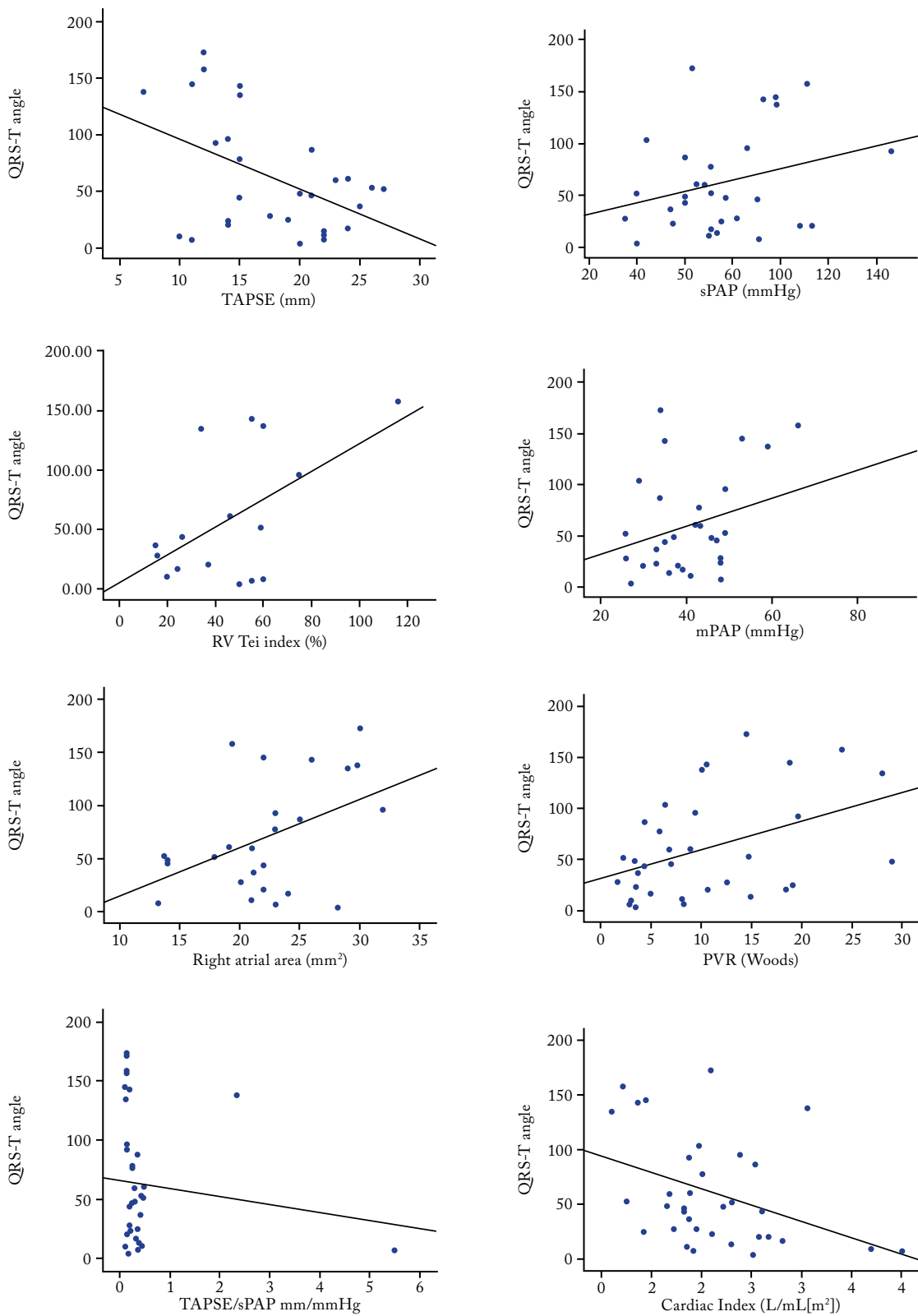


Figure 2. The correlations between the fQRS-T angle and echocardiographic and hemodynamic variables. fQRS-T: Frontal QRS-T.

and also affects adverse cardiovascular outcomes and overall fatality rates in CTEPH patients. Our study showed that the fQRS-T angle was negatively associated with the TAPSE and TAPSE/sPAP ratio, while it was positively correlated with RV Tei index and RAA in CTEPH patients. Among hemodynamic data, sPAP, mPAP, and PVR correlated positively with the fQRS-T angle, while CI was negatively correlated with the fQRS-T angle. However, there was no significant association between the fQRS-T angle and clinical and laboratory characteristics in patients with CTEPH.

Under normal circumstances, the left ventricular (LV) mass is higher than the RV mass, and RV electrical activity is concealed by LV.^[10] Pulmonary hypertension results in RV pressure overload and RV hypertrophy. As RV mass increases, RV contributes to ventricular depolarization and QRS axis changes. The course of the T-axis becomes divergent to QRS-axis and the spatial QRS-T (sQRS-T) angle increase with elevated PH.^[11] It was previously shown that, even in the very early phases of PH, the sQRS-T angle was elevated in rats.^[10] Henkens et al.^[12] also demonstrated that the sQRS-T angle was greater in patients with chronically elevated RV pressure compared with controls.

In the current study, we investigated the clinical, echocardiographic, and invasive hemodynamic correlates of fQRS-T angle CTEPH patients. We were unable to demonstrate a correlation between clinical variables and fQRS-T angle in patients with CTEPH. The inadequate significance can be attributed to the small sample size used in our study. However, we were able to find significant associations between echocardiographic variables including TAPSE, TAPSE/sPAP ratio, RV Tei index, and RAA and fQRS-T angle. Previously, similar to our findings, the QRS-T angle was demonstrated to be linked to echocardiographic variables such as SPAP, dimension of RA and RV, and RV systolic dysfunction and impaired diastolic function in patients with CTEPH.^[7] We showed that the fQRS-T angle was negatively associated with TAPSE and TAPSE/sPAP ratio. As TAPSE estimates RV contractile function, an increase in fQRS-T angle CTEPH patients may correspond to RV systolic dysfunction. Recently, a new prognostic parameter was included in the current PH guidelines. The TAPSE/sPAP ratio, which is a surrogate non-invasive marker of RV-PA coupling and provides information about RV diastolic function, was

demonstrated to be a significant prognostic variable in PH patients.^[13,14] An increase in the fQRS-T angle was also found to be linked to a reduction in TAPSE/sPAP ratio in our study. Therefore, we can speculate that an increase in fQRS-T angle in patients with CTEPH may correspond to impaired both RV diastolic and systolic function. Another parameter that reflects the overall function of the RV is the RV Tei index. The RV Tei index has been shown to be increased in patients with connective tissue-associated-PAH due to RV diastolic dysfunction and decreased myocardial contractility of RV.^[15] Similarly, we showed that the RV Tei index was elevated in CTEPH patients and an elevation in the fQRS-T angle corresponded to an increase in RV Tei index of CTEPH patients. Additionally, RAA has been shown to be a valuable prognostic factor in PH patients. The mortality of PH patients increases in patients with elevated values of RAA.^[4] In the current study, an increase in fQRS-T angle was linked to an increase in RAA. Our results are consistent with the findings of Sakhnova et al.^[7] showing that the QRS-T angle is related to elevated RA size.

In this study, we also examined the correlations between the fQRS-T angle and invasive hemodynamic data in CTEPH patients. The sPAP, mPAP, and PVR correlated positively, whereas CI was negatively correlated with the fQRS-T angle. The positive correlation between sPAP, mPAP, and PVR and fQRS-T angle is comprehensible as an increase in PA pressures and PVR results in an increase in RV mass and a change in QRS and T-axis, resulting in an increased QRS-T angle.^[11] Chronic pressure and volume overload on RV in patients with PH modify the geometry of RV. As a result, RV occupies more space in the pericardium and causes paradoxical interventricular septum movement, thereby leading to a decrease in LV volume at end-diastole.^[16] The decrease in LV diastolic volume at end-diastole results in altered LV stroke volume as explained by the Frank-Starling mechanism.^[17] This may explain the negative correlation between CI and fQRS-T angle.

Nonetheless, this study has several limitations. First, our study has a single-center, retrospective design. Second, since CTEPH is a rare condition, the number of patients is limited. Although multi-center studies involving more patients on this subject are needed, we believe that our study may be a pioneer for further studies on this subject. In addition, although we have long-term follow-up data, the impact of the

fQRS-T angle on prognosis in CTEPH patients is unclear due to the small number of subjects. Another limitation of our study was the utilization of an fQRS-T angle instead of an sQRS-T angle. However, the fQRS-T angle has been used instead of the sQRS-T angle in studies on cardiovascular diseases. The main reason for this is that sQRS-T angle measurement is complicated and necessitates sophisticated computer programs. On the contrary, the fQRS-T angle can be simply calculated from the automatic description of the ECG machine.

In conclusion, ECG seems to be a tool that should not be ignored in the evaluation of CTEPH patients. In these patients, the fQRS-T angle, which can be computed simply by ECG, is negatively correlated with TAPSE, TAPSE/sPAP ratio, and CI, while it is positively correlated with RV Tei index, RAA, sPAP, mPAP, and PVR, which are important prognostic factors in patients with PH.

Ethics Committee Approval: The study protocol was approved by the Dokuz Eylül University Faculty of Medicine Ethics Committee (date: 29.03.2023, no: 2023/10-14). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, writing the article: A.Ç., M.K.; Design: M.K., B.A.; Control/supervision: B.A.; Data collection and/or processing: Z.K., D.S.; Analysis and/or interpretation, materials: A.Ç., Z.K.; Critical review: B.A., B.Ş.; References and fundings: A.Ç., B.Ş.

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