

ORIGINAL ARTICLE

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The Role of the presence of fragmented QRS in predicting disease severity in patients with pulmonary hypertension

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Abstract

Pulmonary arterial hypertension is a malignant pulmonary vascular disease primarily caused by increased pulmonary vascular resistance, which leads to right ventricular hypertrophy, fibrosis, right heart failure and death. Fragmented QRS (fQRS) indicates non-homogeneous ventricular activity caused by myocardial fibrosis. This study aims to investigate the importance of fQRS in patients with pulmonary hypertension (PH) and to determine the role of the presence of fQRS in indicating the severity of the disease. The study included 94 (85 patient group 1 PH and 9 patient group 4 PH) patients. The patients were divided into two groups according to the presence of fQRS in their surface electrocardiography (ECG). The patients' laboratory, transthoracic echocardiography, and right heart catheterization parameters were compared between the two groups. FQRS was detected in 55 (58%) patients, and the mean age of these patients was 51.8 ± 18.0 , and 29.1% of them were male. Systolic pulmonary arterial pressure (PAP) measured by transthoracic echocardiography ($p < 0.001$), pulmonary vascular resistance (PVR) ($p < 0.001$) and mean, diastolic, systolic PAP ($p = 0.001$, $p < 0.001$, $p < 0.001$) measured by right heart catheterization were found to be higher in patients with fQRS presence in their surface ECGs. Moreover, fQRS was found to be of high significance in predicting PVR. (95% CI 2.147-6.182; $p < 0.001$). In conclusion, when evaluating patients with pulmonary hypertension, it will be helpful in our clinical practice to assume that patients with fQRS on surface ECG are more affected hemodynamically and to start combination therapy early or follow up on these patients at shorter intervals.

Keywords: Pulmonary hypertension, electrocardiography, fragmented QRS, Pulmonary vascular resistance

Introduction

Pulmonary hypertension (PH) is a devastating and slowly progressing disease that is usually common among young women, diagnosed late and characterized by increased mean pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) [1,2]. Increased PVR leads to right ventricle (RV) hypertrophy, dilatation and fibrosis. Furthermore, it has been demonstrated that fibrosis develops in the RV through cardiac magnetic resonance (MR) in patients with PH. Thus, right heart failure is the most common cause of morbidity and mortality in PH patients [3].

Fragmented QRS (fQRS) is an electrocardiographic (ECG) parameter that shows non-homogeneous ventricular activity that

occurs due to myocardial fibrosis [4]. In addition, fQRS may develop due to irreversible myocardial fibrosis and ischemia or inflammation [4].

Previous studies have demonstrated that fQRS indicates ventricular dysfunction associated with increased myocardial ischemia or fibrosis in many cardiac and non-cardiac diseases, which is the most important cause of increased mortality [5]. However, the use of fQRS in primary PH has not been investigated. Therefore, this study set out to investigate the usefulness of fQRS existence in detecting RV dysfunction in PH patients.

Material and Methods

Study Population

In this retrospective cohort study, we included 94 patients diagnosed with group 1 or 4 PH at our cardiology department between 2016 and 2021. 85 patients (57 idiopathic, 11 congenital,

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17 scleroderma) were in group 1 pulmonary hypertension (PH) and 9 patients were in group 4 PH. Right heart catheterization (RHC) is the gold standard for the diagnosis and classification of PH. PH is a mean PAP greater than or equal to 20 mm Hg by RHC measured at rest [6]. PH patients are divided into five groups [7]. Group 1 includes patients with pulmonary arterial hypertension (PAH), Group 2 includes patients with PH due to left heart diseases, Group 3 includes patients with PH due to pulmonary diseases, Group 4 includes patients with chronic thromboembolic pulmonary hypertension (CTEPH) and Group 5 includes patients with PH due to unknown mechanism or multifactorial PH [7].

Pulmonary arterial hypertension (PAH) (group 1) is defined as a pulmonary capillary wedge pressure (PCWP) equal to or lower than 15mmHg and PVR above two wood units (WU) without other precapillary PH causes such as pulmonary diseases, chronic thromboembolic pulmonary hypertension (CTEPH) or rare diseases, which can be distinguished hemodynamically with the presence of precapillary PH [6]. Almost half of the PAH patients have idiopathic, hereditary or drug-associated PAH. PAH can also result from systemic sclerosis [8]. Idiopathic PAH is a sporadic disease without any family history of PAH or known triggering factors [7]. CTEPH (group 4) is a disease characterized by chronic thromboembolic lesions in the pulmonary arteries despite effective antithrombotic treatment for a minimum of three months [9]. We selected our patients according to these definitions. Most of the patients in our study had PAH (idiopathic, congenital heart disease or scleroderma), while only a few had CTEPH. After hemodynamic examination, all patients were treated according to the current guidelines.

The patients' baseline demographics, such as age and sex, were analyzed. Next, the detailed etiologies of the patients in Group 1 PH were determined and differentiated. Furthermore, two different cardiologists analyzed the surface ECGs of all patients. Then, it was determined whether there was a difference in demographic, echocardiographic, and RHC characteristics between patients with and without fQRS. Finally, the drugs used by all patients were recorded.

According to the guidelines, the parameters of the transthoracic echocardiography (TTE) of all patients (left ventricular end-systolic and end-diastolic diameter, degree of tricuspid regurgitation and systolic pulmonary artery pressure) were recorded. The ejection fraction (EF) was calculated using a modified Simpson's method. Biochemical tests [hemoglobin, creatinine, brain natriuretic peptide (BNP), neutrophil to lymphocyte ratio] were performed in our hospital laboratory.

Exclusion criterias for the study group were as follows: prior myocardial infarction, thyroid disorder, cardiac implantable electronic device, left ventricular dysfunction, hypertrophic cardiomyopathy, systemic hypertension, left bundle branch block, electrolyte disturbance, atrial fibrillation, medications that might affect the ECG such as; beta blockers, non-dihydropyridine calcium channel blockers, digoxin, amiodaron, and propafenone. Patients who had not undergone RHC were also excluded.

The local ethics committee approved the study (Antalya Education and Research Hospital, Protocol No:2022/147 Decision No:9/13, April 28, 2022).

Electrocardiography

Patients' ECGs were recorded immediately prior to catheterization. A 12-lead surface ECG (Nihon Kohden Corporation, Cardiofax M Model ECG-1250) was recorded in the supine position at a voltage of 10 mm/s, a paper speed of 25mm/s and an AC filter of 60Hz. Some of the intervals, axes, and heart rates were evaluated from the standard ECG, and the presence of fQRS was examined on the ECG. The fQRS presence was determined in the presence of an extra R wave (R') or notches in the nadir of the R wave or the S wave, or in the presence of >1 R' (fragmentation) in two contiguous leads, corresponding to a large coronary area and the presence of different RSR' patterns with or without Q-waves (Figure 1).

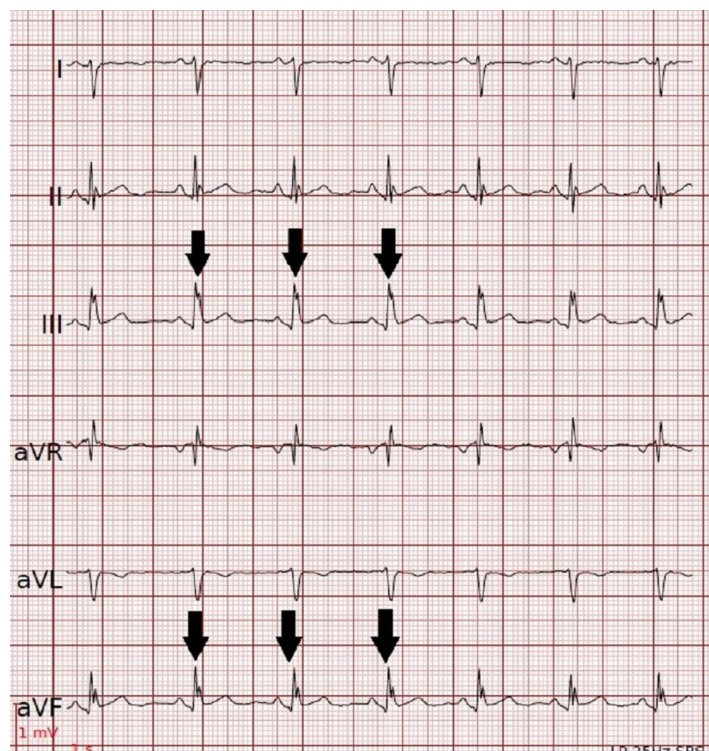


Figure 1. An example of the illustration and presence of fragmented QRS. (Arrows indicate the presence of fragmented QRS in leads D3 and AVF)

Right heart catheterization

Patients suspected of having PAH secondary to TTE were taken to the catheterization laboratory for RHC. First, all patients were informed about the procedure and their written consent was obtained. The patients were then taken to the laboratory for catheterization. Cardiac rhythm, rate and blood pressure of all patients were recorded before the intervention. Because volume status can affect hemodynamic measurement, patients remained euvoletic prior to the procedure. Venous access was obtained via a 7 French (Fr) sheath via the femoral vein. A flexible balloon catheter was then inserted through the 7 Fr sheath. PCWP, PAP, right atrium (RA) and RV pressure were measured using a flexible balloon-tipped catheter. All pressures were recorded as the average of three separate measurements obtained. Measurements were used to calculate cardiac index (CI), diastolic pressure gradient (DPG), transpulmonary pressure gradient (TPG) (the difference between mean PAP and PCWP), or PVR.

All patients were diagnosed with RHC results according to standard

ESC criteria. Blood samples were taken from the intracardiac chambers to identify and quantify shunts between the systemic and pulmonary circulation, to measure the mixed venous oxygen saturation (SvO₂) and to calculate the cardiac output (CO) using the Fick method for large vessels and pulmonary arteries. CI was calculated using the formula: CI (L/min./m²) = CO (L/min) / body surface area (m²) and PVR was calculated as the ratio of TPG and CO. After baseline hemodynamics were obtained, vasoreactivity was assessed to identify patients with PAH.

Statistical Analysis

Statistical analyses were performed with SPSS 24.0 (Statistical Package, Version 24.0). In descriptive findings, categorical variables were presented as frequency and percentages; continuous variables were presented as mean±standard deviation.

Univariate analyses were performed using Chi-square statistics for categoric items such as fQRS existence, and the t-test was used for continuous variables in the independent groups. After univariate analyzes, we performed a multivariate analysis to found variables [age, sex (male), fragmented QRS present, tricuspid regurgitation, left ventricular diastolic and systolic diameter] independently associated with higher PVR. All statistical tests were two-tailed. A p-value of less than 0.05 was considered to show statistically significant results.

Results

The study included a total of 94 patients diagnosed with group 1 or group 4 PH after RHC. Patients were divided into two groups according to the presence of fQRS on their surface ECGs. The baseline demographics of the study group, transthoracic echocardiography, RHC characteristics, and biochemical parameters are described in Table 1.

Baseline patient demographics, such as age and gender, were analyzed. fQRS was detected on surface ECG in 55 patients and not in 39 patients. The mean age was 51.8±18.0 in the group with fragmented QRS, while it was 58.9±12.9 in the group without fQRS (p=0.035). In addition, 29.1% of the fQRS group and 15.4% of the non-fQRS group were male (p=0.122) (Table 1).

The detailed etiologies of the patients in Group 1 PH were determined and differentiated. Regarding the subgroups of patients with pulmonary hypertension, among patients with fQRS, 67.3% had idiopathic PH, 10.9% had PH due to congenital heart disease, 12.7% had scleroderma-associated PH, 9.1% had CTEPH; whereas among patients without fQRS, 51.3% had idiopathic PH, 12.8% had PH due to congenital heart disease, 25.6% had sclerodermaassociated PH, and 10% had CTEPH (p=0.366).

Of the patients found to have a fragmented QRS, 47.3% were taking macitentan, 7.3% ambrisentan, 32.7% bosentan, and 9.1% riociguat. 3.6% of these patients underwent surgery for CTEPH. Of the patients who did not detect a fragmented QRS, 46.2% were taking macitentan, 12.8% ambrisentan, 25.6% bosentan, and 5.1% riociguat. 10.3% of these patients underwent surgery (p=0.529).

In the patient group with fragmented QRS, the left ventricle diastolic diameter (LVDD) measured by transthoracic

echocardiography (TTE) was 42.6±5.6 mm, left ventricle systolic diameter (LVSD) was 27.3±4.4 mm while LVDD was 43.8±4.9 mm, LVSD was 28.2±4.4 mm in the group without fQRS (p:0.249, p:0.194). The sPAP measured with TTE was 81.7 ±22.4 mmHg in the fQRS group, while it was 62.7±16.1 mmHg in the non-fQRS group (p<0.001).

Table 1. Baseline demographics, transthoracic echocardiography and right heart catheterization characteristics and laboratory findings

Variables	Fragmented QRS (-) (n=39)	Fragmented QRS (+)(n=55)	P value
Age, years	58.9±12.9	51.8±18.0	0.035
Male, % (n)	15.4(6)	29.1(16)	0.122
Subgroup, % (n)			
Idiopathic	51.3(20)	67.3(37)	0.366
CTEPH	10.3(4)	9.1(5)	
Congenital	12.8(5)	10.9(6)	
Scleroderma	25.6(10)	12.7(7)	
Treatment, % (n)			
Macitentan	46.2(18)	47.3(26)	0.529
Ambrisentan	12.8(5)	7.3(4)	
Bosentan	25.6(10)	32.7(18)	
Riociguat	5.1(2)	9.1(5)	
Surgery	10.3(4)	3.6(2)	
Transthoracic echocardiography			
LVDD, mm	43.8±4.9	42.6±5.6	0.249
LVSD, mm	28.2±4.4	27.3±4.4	0.194
TR, % (n)			
Grade 1	17.9(7)	7.8(4)	0.070
Grade 2	30.8(12)	17.6(9)	
Grade 3	51.3(20)	74.5(38)	
sPAPECHO, mm hg	62.7±16.1	81.7±22.4	<0.001
Right heart catheterization			
PVR, WU	4.5±2.3	9.4±4.9	<0.001
QP	4.3±2.7	4.6±1.8	0.524
Systolic PAP, mm hg	60.5±26.8	77.9±25.6	<0.001
Diastolic PAP, mm hg	24.1±13.8	30.5±11.4	<0.001
Mean PAP, mm hg	39.6±17.7	60.1±79.8	0.001
Laboratory tests			
BNP, pg/ml	1573.0±1710	2540.0±3892.8	0.516
NLR	4.7±6.8	4.4±6.1	0.815
Hb, g/dl	12.8±1.9	13.5±2.7	0.051
Creatinine, mg/dL	1.0±0.6	1.0±0.5	0.391

CTEPH: Chronic Thromboembolic Pulmonary Hypertension; LVDD: left ventricle diastolic diameter; LVSD: Left ventricle systolic diameter; TR: Tricuspid regurgitation; sPAPECHO: estimated systolic Pulmonary arterial pressure by transthoracic Doppler echocardiography; PVR: Pulmonary vascular resistance; QP: Pulmonary flow; PAP: Pulmonary arterial pressure; BNP: Brain natriuretic peptide NLR: Neutrophil to lymphocyte ratio; Hb: Hemoglobin

As for the results of right heart catheterization, the mean PAP in the fQRS group was 60.1±19.8 mmHg, while in the non-fQRS group it was 39.6±17.7 mmHg. The systolic PAP was 77.9±25.6 mmhg in the group with fQRS and 60.5±26.8 mmhg in the group without fQRS. The diastolic PAP was 30.5±11.4 mmHg in the group with fQRS, while it was 24.1±13.8 mmHg in the group without fQRS (p<0.001). The PVR was 9.4±4.9 WU in the fQRS group, while it

was 4.5±2.3 WU in the group without fQRS (p<0.001).

The biochemical tests (hemoglobin, creatinine, BNP, neutrophil to lymphocyte ratio) were similar between groups (All p-values were >0.05).

We performed a multivariate analysis with variables such as Age, gender, Fragmented QRS, TR, LVDD, LVSD, and BNP to find variables independently associated with higher PVR. After analysis, fQRS was found to be of high importance in predicting PVR (Table 2).

Table 2. Univariate and multivariate linear regression model created to predict PVR, fQRS is at a high significance level

Variables	Univariate				Multivariate			
	β	95% CI		p-value	β	95% CI		p-value
Age, years	-0.042	-0.148	0.064	0.435	-0.032	-0.099	0.036	0.355
Sex (male)	4.716	0.677	8.755	0.023	0.307	-2.210	2.825	0.808
Fragmented QRS present	5.844	2.575	9.112	0.001	3.994	1.801	6.188	<0.001
TR	-0.104	-2.705	2.496	0.937	-0.115	-1.991	1.630	0.868
LVDD	-0.268	-0.612	0.076	0.125	0.019	-0.375	0.145	0.381
LVSD	-0.185	-0.603	0.233	0.381	0.126	-0.305	0.344	0.906

TR: Tricuspid regurgitation degree; LVDD, Left ventricle diastolic diameter; LVSD: left ventricle systolic diameter; BNP: Brain natriuretic peptide

Discussion

Pulmonary hypertension is a rare but progressive disease [6]. There are many systemic diseases and genetic mutations in their etiology. It is divided into five groups. The first group includes PAH patients [8]. The fourth PH group includes CTEPH patients. Most of the patients in our study had group 1 PH (idiopathic, congenital heart diseases or scleroderma), whereas only a few were in group 4 (CTEPH).

Vasoconstriction, vascular remodeling and thrombosis play a role in the physiopathology of PAH [2]. PVR is elevated, PCWP is normal at the onset of the disease, while CO is normal or decreases. In later stages, CO decreases, right ventricular afterload increases, RV hypertrophy and dilatation occur, intraventricular septum (IVS) shifts to the left, and RV ischemia develops [10].RV ischemia causes fibrosis in the RV in time. Cardiac MR examinations of PH patients have demonstrated that diffuse right heart fibrosis has developed. The post-mortem autopsies of idiopathic PAH patients also revealed fibrosis, especially more in the junction of the RV and septum [11]. Survival is reduced in patients who develop cardiac fibrosis.

Early diagnosis and treatment of PH are very important. However, its symptoms are not specific, and they are mild initially. Therefore, the disease can be easily overlooked early without clinical suspicion. As the disease progresses in time, severe symptoms occur. ECG, TTE, lung x-ray, respiratory function tests, arterial blood gas, ventilation-perfusion scintigraphy, computed tomography, MRI, pulmonary angiography, abdominal ultrasonography, blood and immunological tests and RHC can be used for its diagnosis [12]. RHC is the gold standard for determining disease severity, underlying cause, and definitive diagnosis to plan and manage treatment and show prognosis [13]. However, it is an invasive and expensive method and should be performed by experienced operators. Our study included patients diagnosed during RHC and for whom treatment was started in our hospital.

Cardiac MRI, widely used today, is the gold standard noninvasive method for examining the structure, volume, and functions of the right ventricle, which is crucial for the diagnosis and prognosis of PH [14]. Nevertheless, this is yet another expensive and inaccessible method. Therefore, we did not show right ventricular fibrosis with cardiac MRI either, which was one of the limitations of our study.

It is challenging to use the RHC and cardiac MRI in daily routine. TTE is a simple and widely available diagnostic tool. TTE can demonstrate RV dysfunction and pulmonary hypertension, but it can be easily missed unless there is sufficient TR or, specifically, PH is suspected for diagnosis [15]. So, more practical markers that correlate with cardiac prognosis are needed. ECG is a simple and easily accessible method, whereas there are few studies about the ECG's role in PH patients [15]. Hemodynamic, autopsy, and MRI studies have demonstrated a significant correlation between hemodynamic state, RV hypertrophy, and ECG changes [16].

Studies are showing the effects of ECG changes on the disease. P Pulmonale, right axis shift, RV hypertrophy, RV strain, right bundle branch block, and prolonged QTc are typically seen and examined in ECG in patients with PH [17,18]. Moreover, MRI studies confirmed that R wave amplitude in lead V1 and P wave amplitude in lead D2 demonstrate right ventricular hypertrophy and RV dilatation [19]. In addition, It has also been shown that these ECG parameters are correlated with hemodynamic values such as PAP and PVR measured during RHC. [19]. Kanemato et al. showed that R/S ratio and R wave amplitude on V1 was significantly correlated with sPAP. This study also demonstrated that R wave amplitude and R/S ratio were significantly correlated with CI [20]. Some studies have examined the relationship between ECG changes caused by the disease and prognosis outcomes. Bossone et al. showed that ECG changes in PH patients were associated with shorter survival. A p wave amplitude of 0.25 mv or greater on D2 lead and Qr pattern on V1 lead decreased survival [21]. During our literature review, however, we could not find a study about the

presence and importance of fQRS in PH patients. That is why we intended to conduct this study.

fQRS was defined by an additional R wave (R') or notching within the QRS complex on two adjacent leads on ECG [22]. There are many mechanisms responsible for QRS fragmentation. An implicated mechanism is explained by the inhomogeneous impulse conduction of the ventricles due to myocardial scarring. So, fQRS is an ECG finding showing the presence of myocardial scar and ischemia [4]. Moreover, changes in Purkinje fibers after myocardial infarction and myocardial fibrosis modify the QRS complex morphology on ECG and fragmentation occurs. This new parameter is called fQRS [23].

SPECT studies demonstrated that fQRS was associated with significantly greater perfusion and functional abnormalities than Q wave, and even its sensitivity was higher than that of Q wave [24]. It has been useful in demonstrating poor collateral circulation in patients with chronic stable angina and predicting mortality in patients with congestive heart failure. In cardiac diseases, it correlates with subclinical left ventricular dysfunction or scarring and predicts a higher incidence of ventricular arrhythmias. Several studies have demonstrated that it is critical to predicting unfavorable arrhythmic events in arrhythmic syndromes [25-27]. Therefore, the presence of this ECG parameter is important in cardiac patients with arrhythmia predisposition. Moreover, in the presence of this ECG parameter in individuals with arrhythmic syndrome, follow-up intervals should be shortened.

The importance of fQRS in valve diseases was investigated. fQRS was associated with myocardial dysfunction, PH and severity of the stenosis in patients with mitral stenosis. In addition, it was found to be superior to other TTE parameters in predicting left ventricular hypertrophy in patients with aortic stenosis [28,29].

Also, the importance of fQRS in systemic connective tissue diseases was investigated. For example, in patients with systemic sclerosis, myocardial fibrosis indicates cardiac involvement and cardiac events that may occur. Studies show that fQRS can allow early detection of myocardial fibrosis before symptoms are manifested in these patients [30].

The association between fQRS and cardiac and non-cardiac diseases has been proven in several studies in the literature. Also, it has been demonstrated to play a critical role in the characterization, monitoring, and prognosis of numerous diseases.

In our study, the sPAP measured with TTE, the mean, systolic and diastolic PAP and PVR measured during RHC were significantly higher in the PH patients who were found to have fQRS on a routine 12-lead ECG compared to those without fQRS. Therefore, while evaluating PH patients, it will help us in our clinical practice to assume that patients having fQRS on surface ECG are hemodynamically affected more and intensification of therapy or shorter follow-up may be considered in these patients.

Study limitations

Firstly, cardiac MRI was not used to detect fibrosis in the right ventricle in our study. Another major limitation was the retrospective design of the study. So, patients could not be

followed up for forthcoming arrhythmic events. As the patients were not followed up for a long term, there is no information about the prognosis of the group where fQRS was present and the correlation between fQRS and future cardiac events.

Conclusion

Examination of ECGs for the presence of fQRS in patients who follow up for PAH and CTEPH is an important and valuable parameter to detect high-risk patients in the early period.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

The local ethics committee approved the study (Antalya Education and Research Hospital, Protocol No:2022/147 Decision No:9/13, April 28, 2022).

References

1. Barst RJ, McGoon M, Torbicki A et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol. 2004;43:40-7.
2. Karabiyikoglu G. Pulmonary arterial hypertension. In Karabiyikoglu G. Ed. Pulmoner Hipertansiyon. Ankara, Antip Printing House; 2007;112-130p.
3. Alparslan B, Sivrioglu AK. The role of cardiac MRI in the diagnosis and follow-up of pulmonary hypertension. Trd Sem 2018;6:300-311.
4. Supreeth RN, Francis J. Fragmented QRS- Its significance. Indian Pacing Electrophysiol J. 2020;20:27-32.
5. Cetin MS, Cetin EH, Arisoy F, et al. Fragmented QRS complex predicts in hospital adverse events and long term mortality in patients with acute pulmonary embolism. Ann Noninvasive Electrocardiol. 2016;21:470-8.
6. Humbert M, Kovacs G, Hoeper MM et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43:3618-731.
7. Galie N, Humbert M, Vchieri JL et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Kardiologia Pol. 2015;73:1127-206.
8. Humbert M, Sitbon O, Chaouat A et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006;173:1023-30.
9. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. Chest. 1982;81:151-8.
10. Lee SH, Rubin LJ. Current treatment strategies for pulmonary arterial hypertension. J Int Med. 2005;258:199-215.
11. Yoshihara S, Suzuki S, Matsunaga M et al. Right ventricular fibrosis in idiopathic pulmonary arterial hypertension. Acta Cardiol 2020;75:263-4.
12. Ozturk O, Sahin U. Pulmonary arterial hypertension: diagnosis and treatment. S.D.U. Journal of the Faculty of Medicine. 2009;16:39-47.
13. Penning S, Robinson KD, Major CA, Garite TJ. A comparison of echocardiography and pulmonary artery catheterization for evaluation of pulmonary artery pressures in pregnant patients with suspected pulmonary hypertension. Am J Obstet Gynecol. 2001;184:1568-70.
14. Alassas K, Mergo P, Ibrahim ES et al. Cardiac MRI as a diagnostic tool in pulmonary hypertension. Future Cardiol. 2014;10:117-30.
15. Ahearn GS, Tapson VF, Rebeiz A, Greenfield JC. Electrocardiography to define clinical status in primary pulmonary hypertension and pulmonary arterial hypertension secondary to collagen vascular disease. Chest. 2002;122:524-7.

16. Kopeć G, Tyrka A, Miszański-Jamka T. et al. Electrocardiogram for the diagnosis of right ventricular hypertrophy and dilatation in idiopathic pulmonary arterial hypertension. *Circulation J*. 2012;76:1744-9.
17. Al- Naamani K, Hijal T, Nguyen V et al. Predictive values of the electrocardiogram in diagnosis pulmonary hypertension. *Int J Cardiol*. 2008;127:214-8.
18. Bonderman D, Wexberg P, Martischniig AM et al. A noninvasive algorithm to exclude precapillary pulmonary hypertension. *Eur Respir J*. 2011;37:1096-103.
19. Cheng XL, He JG, Liu ZH et al. The value of the electrocardiogram for evaluating prognosis in patient with idiopathic pulmonary arterial hypertension. *Lung*. 2017;195:139-46.
20. Kanemoto N. Electrocardiographic and hemodynamic correlations in primary pulmonary hypertension. *Angiology*. 1998;39:781-7.
21. Bossone E, Paciocco G, Iarussi D et al. The prognostic role of the ECG in primary pulmonary hypertension. *Chest*. 2002;137:376-87.
22. Jain R, Singh R, Yamini S, Das MK. Fragmented ECG as a risk marker in cardiovascular diseases. *Curr Cardiol Rev*. 2014;10:277-86.
23. Friedman PL, Fenoglio JJ, Wit AL. Time course for reversal of electrophysiological and ultrastructural abnormalities in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs. *Circulation Res*. 1975;36:127-44.
24. Michael MA, El Masry H, Khan BR et al. Electrocardiographic signs of remote myocardial infarction. *Prog Cardiovasc Dis*. 2007;50:198-208.
25. Bonakdar H, Moladoust H, Kheirikhah J et al. Significance of a fragmented QRS complex in patients with chronic total occlusion of coronary artery without prior myocardial infarction. *Anatol J Cardiol*. 2016;16:106-12.
26. Mizusawa Y, Wilde AA. Brugada syndrome. *Circ Arrhythm Electrophysiol*. 2012;5:606-16.
27. Tschabrunn CM, Haqqani HM, Santangeli P et al. 12 lead electrocardiogram to localize region of abnormal electroanatomic substrate in arrhythmogenic right ventricular cardiomyopathy. *JACC Clin Electrophysiol*. 2017;3:654-65.
28. Yuce M, Davutoglu V, Ozbala B. et al. Fragmented QRS is predictive of myocardial dysfunction, pulmonary hypertension and severity in mitral stenosis. *Tohoku J Exp Med*. 2010;220:279-83.
29. Açıkgöz E, Yaman B, Açıkgöz SK. et al. Fragmented QRS can predict severity of aortic stenosis. *Ann Noninvasive Electrocardiol*. 2015;20:37-42.
30. Bayar N, Çay HF, Erkal Z et al. The importance of fragmented QRS in the early detection of cardiac involvement in patients with systemic sclerosis. *Anatol J Cardiol*. 2015;15:209-12.