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Uric Acid and P-Wave Dispersion in Subjects with Heart Failure

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Abstract: Uric acid used as a marker of cardiovascular risk, which is associated with oxidative stress and inflammation. P-wave dispersion (PWD) is an electrocardiographic measure, which shows heterogeneity of atrial depolarization. It has demonstrated that there is an association of increased PWD with atrial fibrillation. This article's goal was to investigate the relationship between PWD and uric acid in subjects with heart failure (HF). Methods This descriptive, cross-sectional study included a total of 315 stable HF outpatients. The subjects were classified into two groups by their PWD: the normal PWD group consisted of subjects with a PWD lower than 40 ms (n = 201), and the increased PWD group consisted of subjects with a PWD higher than or equal to 40 ms (increased PWD) (n = 114). Results Significantly higher uric acid levels determined in the increased PWD group, in comparison with the normal PWD group (7.4 ± 1.6 mg/dL, vs. 6.5 ± 1.6 mg/dL $p < 0.001$). Univariate analyses revealed an association between uric acid, blood urea nitrogen, systolic pulmonary artery pressure, left atrial diameter, and increased PWD. In multivariate logistic regression analysis, there was an association of uric acid level (OR: 1.293; 95% CI: 1.106-1.511, p: 0.001), systolic pulmonary artery pressure (OR: 1.027; 95% CI: 1.011-1.044, p: 0.001), and left atrial diameter (OR: 1.754; 95% CI: 1.028-2.992, p: 0.039) with PWD. The receiver operating characteristics (ROC) curve analysis demonstrated that the optimal cut-off level of uric acid for predicting increased PWD was ≥ 7.1 mg/dL with a specificity of 77 percent and a sensitivity of 81 percent. Conclusion Our study results suggest that serum uric acid levels independently correlated with PWD in subjects with HF.
Keywords: P-wave dispersion; uric acid; heart failure

INTRODUCTION

Heart failure (HF) represents a complex clinical syndrome, which is related to high mortality and morbidity rates (Bui et al, 2011). P-wave dispersion (PWD) described as the difference between the longest and shortest P-wave durations on 12-lead electrocardiography (ECG). Furthermore, PWD is a non-invasive marker of heterogeneity of atrial depolarization (Aizawa et al, 2017). Several studies have shown that increased PWD can predict atrial fibrillation (AF) (Pérez-Riera et al, 2016). AF and HF commonly coexist. When they exist in conjunction, each condition has a more severe course with an increased risk of mortality (Carlisleet al, 2019). Previous studies have demonstrated that oxidative stress and inflammation can play a significant part in the development of AF in patients with HF (Oikonomou et al, 2019).

Uric acid, which represents the final product of purine metabolism, is a surrogate marker of inflammation and oxidative stress (Bergamini et al, 2009). The xanthine oxidase enzyme mediates its production. A correlation of increased levels of uric acid with oxidative stress, endothelial dysfunction, and cardiovascular risk has

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revealed (Borghi et al, 2018; Shao et al, 2019; Zhao et al, 2012). Nevertheless, a relationship of increased uric acid levels with the development of AF has shown in a few studies. Best of our knowledge, the relationship between uric acid levels and PWD, which is a predictor of AF, has not been studied in subjects with HF in the literature. This article's goal was to examine the relationship between PWD and uric acid levels in HF subjects.

MATERIALS AND METHOD

Patients and Methods

This descriptive, cross-sectional research involved a total of 315 (142 females and 173 males) outpatients with the New York Heart Association (NYHA) functional class II, III, and NYHA ambulatory functional Class IV HF. Left ventricular systolic dysfunction (a left ventricular ejection fraction of < 50 percent) determined in all of the subjects. 12-lead ECG and blood samples obtained on the same day. Patients with thyroid dysfunction, gout, infectious diseases, atrial fibrillation, connective tissue diseases, neoplastic processes, neurologic disorders, end-stage renal disease, and patients taking drugs, which could influence uric acid metabolism (except for diuretics), were not included in the research.

Written informed consent received from every subject. The Ethics Committee of Cumhuriyet University (Sivas, Turkey) approved the study protocol. The research carried following the principles of the Declaration of Helsinki.

ECG examination

Twelve-lead ECG acquired following a 10-min rest with a 20 mm/Mv amplitude and 50 mm/sec rate with the standard lead positions. The ECG readings were evaluated by two cardiologists, blinded to the patient data. P-wave duration measurement performed in all leads from the start of the P-wave, which defined as the point at the initial deflection of the P-wave crossed the isoelectric line, to the ending of the P-wave, which defined as the point at the final deflection of P-wave crossed an isoelectric line. Increased PWD defined as a PWD of ≥ 40 ms(Dilaveris,1998). Increased PWD is associated with AF. Patients in the current research classified into two groups based on their PWD: the normal PWD group with a PWD < 40 ms (n = 201) and the increased PWD group with a PWD ≥ 40 ms (n = 114).

Transthoracic echocardiography examination

All patients underwent transthoracic echocardiography (TTE). TTE examinations performed using a 2.5 MHz transducer and a Vivid 7 Dimension® (GE Vingmed Ultrasound AS, N-3190 Horten, Norway) echocardiography device. The measurements carried out in a left-side decubitus position following a rest time of min through the standard parasternal long axis, short axis, and apical four- and five-chamber view windows. The measurements of the interventricular septum thickness, left ventricular posterior wall thickness, left ventricle (LV) end-systolic diameter, and LV end-diastolic diameter was made just below the mitral valve in the parasternal long-axis view using M-mode examination. In the parasternal long-axis view, M-mode examination used to measure the left atrium size. The left ventricular ejection fraction computed using the biplane Simpson's method from apical four-chamber and two-chamber views following the recommendation of the American Society of Echocardiography (Lang RM et al., 2005). The calculation of the systolic pulmonary artery pressure (SPAP) was performed through the peak velocity of tricuspid regurgitation and estimated right atrial pressure (Lancelotti et al, 2010).

significant statistically

RESULTS AND DISCUSSION

Table 1. Baseline Characteristics of the Patients

Variables	All patients (n=315)	Group 1 (PWD<40ms) (n=201)	Group 2 (PWD≥40ms) (n=114)	p-value
Baseline charecteristics				
Age (yr)	65 ± 12	65±13	66 ±12	0,486
Female	142 (%45)	97(%48)	45(%40)	0,132
Hypertension	190(%60)	122(%61)	68(%60)	0,855
Diabetes mellitus	128(%41)	87(%43)	41(%36)	0,204
CAD(%)	224(%71)	140(%70)	84(%74)	0,440
BMI (kg/m^2)	27±4,0	27±3,7	27±4,4	0,282
ACE/ARB(%)	271(%86)	173(%86)	98(%86)	1,000
Beta blocker(%)	284(%90)	181(%90)	103(%90)	1,000
Thiazides(%)	124(%39)	83(%41)	41(%36)	0,352
Loop diuretics(%)	205(%65)	131(%65)	74(%65)	1,000
Aldosterone anagonists(%)	210(%67)	131(%65)	79 (%69)	0,456
Echocardiographic findings				
LVEF (%)	33±6	33±6	33±7	0,753
LA(cm)	4,5 ±0,5	4,4±0,5	4,6±0,5	**<0,001**
LVEDD(cm)	5,6 ±0,5	5,5 ±0,6	5,6 ±0,6	0,571
SPAP (mmhg)	38±17	34±16	43±16	**<0,001**
Laboratory findings				
Hemoglobin (g/dL)	12,5±2,0	12,5±2,0	12,5±2,0	0,649
BUN(mg/dL)	23 ± 10	21 ± 10	25 ± 10	0,004
Creatinine (mg/dL)	1,0±0,3	1,0±0,3	1,0±0,3	0,092
Sodium (mmol/L)	136±4	136±4	136±4	0,765
Potassium(mmol/l)	4,3±0,5	4,3±0,5	4,2±0,5	0,133
WBC cells/µl	7859±2414	7720±2385	8103±2457	0,177
Platelet (10^{3}x cells/µl)	255±120	255±124	255±114	0,998
Uric acid (mg/dl)	6,8±1,6	6,5±1,6	7,4±1,6	<**0,001**

Abbreviations: PWD, P wave dispersion; DM, diabetes mellitus; CAD, coronary artery disease; BMI, body mass index; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricle ejection fraction; LA, left atrial diameter; SPAP, systolic pulmonary artery pressure; LVEDD, left ventricle end-diastolic diameter, BUN, blood urea nitrogen; WBC, white blood cell.

Three hundred fifteen subjects in total (142 females and 173 males) with an average age of 65 ± 12 years enrolled in the present research. The mean body mass index (BMI) of the patients was 27 ± 4.0 kg/m^2. The BMI values were similar among the males and females in this study. Comorbidities of the study population included hypertension (60%, n = 190), diabetes mellitus (DM) (41%, n = 128), and coronary artery disease (CAD) (71%, n=224). The mean ejection fraction (EF) was 33 ± 6%. Significantly higher uric acid levels determined in the increased PWD group in comparison with the normal PWD group (7.4 ± 1.6 mg/dL, vs. 6.5 ± 1.6 mg/dL $p < 0.001$). The left atrial diameter (LA) and systolic pulmonary artery pressure (SPAP) was also significantly higher (4.6 ± 0.5 vs. 4.4 ± 0.5, $p<0.001$ and 43 ± 16 vs. 34 ±

16, p < 0.001, respectively) in the increased PWD group, in comparison with the normal PWD group. Baseline characteristics, echocardiographic parameters, and laboratory data presented in Table 1.

Table 2. Spearman Correlation Coefficients for PWD

Variable	**PWD level**	**p-value**
LA	0,311	<0,001
LVEDD	0,136	0,016
SPAP	0,266	<0,001
BUN	0,295	<0,001
Creatinin	0,228	<0,001
Uric acid	0,353	<0,001

Abbreviations:PWD, P wave dispersion; SPAP,systolic pulmonary artery pressure; LA, left atrial diameter; LVEDD, left ventricule enddiastolic diameter BUN, blood ure nitrogen

Table 3. Univariate and Multivariate Analyses for Predicting Increased PWD

	Univariate			Multivariate		
Variable	p	OR	(95% Cl)	P	OR	(95% Cl)
Statistically significant variables						
Uric Acid	<0,001	1,374	1,185-1,593	0,001	1,293	1,106-1,511
SPAP	<0,001	1,035	1,020-1,051	0,001	1,027	1,011-1,044
LA	<0,001	2,859	1,747-4,679	0,039	1,754	1,028-2,992
BUN	0,004	1,035	1,011-1,060			
Variables correlating with increased PWD						
Creatinin	0,086	1,812	0,919-3,573			
LVEDD	0,569	1,113	0,760-1,649			

All the variables from Table 1 were examined and only those significant at P < 0.05 level and correlated with PWD are shown in univarite analysis. Multivariate logistic regression analysis including all the variables inunivariate analysis with forward wald method. CI: Confidence interval; OR: odds ratio, PWD, P wave dispersion; SPAP, systolic pulmonary artery pressure; LA,left atrial diameter ; BUN, blood urea nitrogen; LVEDD, left ventriculeenddiastolic diameter

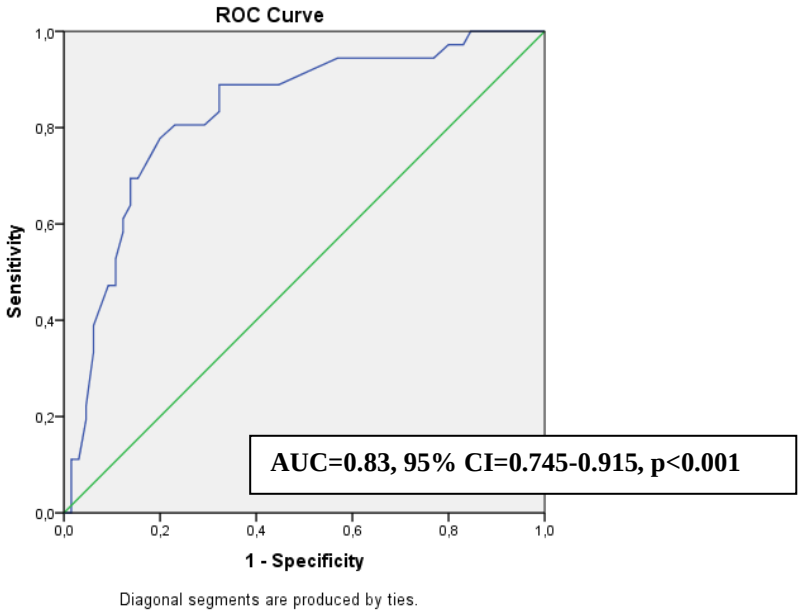

Figure 1. ROC Curve of Uric Acid to Predict Increased PWD

As presented in Table 2, uric acid, blood urea nitrogen (BUN), creatinine, left atrial diameter, SPAP, and left ventricular end-diastolic diameter positively correlated with PWD. Table 3 presents the findings of the univariate and multivariate logistic regression analyses for increased PWD. Uric acid, SPAP, left atrial diameter, and BUN was associated with increased PWD in univariate analyses. In the multivariate logistic regression analysis, uric acid (OR: 1.293; 95% CI: 1.106-1.511, p: 0.001), SPAP (OR: 1.027; 95% CI: 1.011-1.044, p: 0.001), and left atrial diameter (OR: 1.754; 95% CI: 1.028-2.992, p: 0.039) remained correlated with increased PWD after adjusting for the variables that significantly correlated with PWD in the univariate analyses.

The ROC curve analysis indicated that the optimal cut-off level of uric acid for predicting increased PWD was ≥7.1 mg/dl with a specificity of 77% and sensitivity of 81% (AUC = 0.83, 95% CI = 0.745-0.915, p < 0.001, Figure 1).

As far as we know, the current research represents the first study in the literature, which shows an independent correlation between PWD and serum uric acid levels in subjects with HF.

Similar pathophysiological pathways are involved in HF and AF, and the concomitance of these two conditions is associated with mortality (Kotecha et al, 2015). Oxidative stress and inflammation play a significant part in the development of AF in subjects with HF (Zacharia et al, 2019). Uric acid, which is the final product of purine metabolism, represents an important marker of inflammation and oxidative stress. Several studies have suggested a relationship between high uric acid levels and the development of AF (Tamariz et al, 2011; Nyrnes et al, 2014).

P-wave dispersion, which described as the difference between the longest and shortest P-wave duration on 12-lead ECG, represents a non-invasive marker of heterogeneity of atrial depolarization. The increased dispersion of atrial refractoriness has shown to induce reentry, leading to AF(Pérez-Riera et al, 2016). A PWD of 40 ms or higher defined as increased PWD. Dilaveris et al. reported that a PWD value of 40 ms predicted AF with a sensitivity of 83%, a specificity of 85%, and a positive predictive value of 89%(Dilaveris et al,1998).

Increased PWD has associated with certain cardiovascular disorders including cardiomyopathies, rheumatic mitral valve stenosis, stroke and hypertension all of which correlated with a high risk of AF (Dogan et al, 2012; Kocaoglu et al, 2012; Russo et al, 2017; Tsioufis et al, 2019). The current study may indicate that the association between uric acid and the development of AF can be due to increased PWD.

Several studies indicated a correlation between uric acid and PWD under certain clinical conditions. Su et al. investigated the association between PWD and the maximum P-wave duration and rapid deterioration in kidney functions and found an independent association between high uric acid levels and increased PWD (β = 0.281, p = 0.002) (Su et al, 2012). Çakar et al. stated that serum uric acid levels were associated with minimum, maximum, and mean P-wave durations in military jet pilots and transport aircraft aircrew (r = 0.355, p = 0.002; r = 0.318, p = 0.006; and r = 0.422, p < 0.001, respectively) (Çakar et al, 2016).

The association between uric acid and PWD may be due to the relationship between uric acid and the selective increase in atrial oxidative stress. Uric acid is a marker of upregulated xanthine oxidase activity, which leads to the production of reactive oxygen species, which induce atrial tissue injury (Bergamini et al,2009). Furthermore, uric acid production due to microvascular tissue hypoxia may affect the atrial tissue via systemic oxidative stress. Increased xanthine oxidase activity may lead to cardiac dysfunction and the progression of HF by inducing oxidative stress and uric acid production (Borghi et al, 2019; Huang et al, 2019). Several studies have shown that lowering uric acid levels without altering xanthine oxidase activity does not provide clinical benefit (George et al,2006; Ogino et al, 2010). Therefore, xanthine oxidase activity appears to play a significant part in oxidative stress. Depression of cardiac functions and increased oxidative stress may be responsible for atrial fibrosis, which may be associated with increased PWD. Moreover, increased uric acid levels may increase PWD by inducing endothelial dysfunction and activating the renin-angiotensin-aldosterone system (Johnson et al, 2005).

In the present study, SPAP found to be significantly associated with increased PWD. Similarly, Guntekin et al. detected a positive association between SPAP and PWD in patients with mitral valve stenosis (r = 0.295, P = 0.047) (Guntekin et al, 2008). However, in the study by Turhan et al., the decrease in SPAP after mitral balloon valvuloplasty was not found to be associated with a parallel decrease in PWD (Turhan et al, 2002). Based on these findings, we suggest that the relation between SPAP and PWD takes place, as diastolic dysfunction in HF may lead to an increase in pulmonary artery pressure in addition to atrial dilatation and fibrosis. The other possible explanation is that enhanced sympathetic activity in patients with HF may increase both PWD and SPAP to a similar extent (Akutsu et al, 2013; Tukek et al, 2000).

In the present research, the left atrial diameter found to be significantly associated with increased PWD. Some studies have also found similar associations, while some authors have not shown such an association (Ozyigit et al, 2016; Sarvari et al, 2016; Koide et al, 2002; Tukek et al, 2001). P-wave dispersion may be affected by the delay in site-dependent intra-atrial conduction before the onset of left atrial dilatation (Hatam et al, 2014; Gazi et al, 2015). However, increased sympathetic activity may affect the propagation of the sinus impulse in subjects with HF. It has also reported that PWD may be affected by increased left atrial pressure, diastolic changes, and intra atrial oxidative stress (Gudul et al, 2017).

In the current study, BUN and creatinine levels positively correlated with PWD.

However, neither BUN nor creatinine was an independent predictor of increased PWD in multivariate regression analysis. Another study showed an independent association between PWD and deterioration in kidney functions (Su et al, 2012). The association between PWD and kidney functions may be due to subclinical inflammation, endothelial dysfunction, systemic neurohormonal activation, and oxidative stress in patients with kidney disease.

Although the clinical implementation of our findings is a little bit difficult and dubious, the increased levels of uric acid, as an inflammatory biomarker in heart failure, might corrupt the atrial conduction. Our data analysis showed that increased levels of uric acid could be a trigger for atrial arrhythmias. Furthermore, large-scale studies evaluating the impact of drugs interacting with uric acid metabolism on arrhythmias can enlighten this association.

Nonetheless, there are a few limitations of the present research. Firstly, this study has a small sample size. Secondly, we used the manual measurement of P-waves by a magnifying lens rather than a computer-assisted calculation. In previous studies, digital and signal-averaging ECG systems utilized to evaluate PWD more accurately (Tukek et al, 2000; Dilaveris et al, 1999). Thirdly, the current research represents a cross-sectional study and further longitudinal studies required for confirming the relationship between PWD and uric acid. Another limitation was the lack of regular ambulatory ECG monitorization. That is why paroxysmal AF attacks could not be recorded. Finally, it is possible that the left atrial maximal diameter, measured in the present research, does not represent the left atrial size and volume in subjects with HF accurately.

CONCLUSION

In conclusion, our study results suggest an independent association between serum uric acid levels and PWD in subjects with HF. The relationship between increased uric acid levels and the development of AF in subjects with HF can originate from increased PWD. Furthermore, prospective research with larger sample sizes required for confirming this association and demonstrating underlying pathophysiological mechanisms. Such studies would also provide information to prevent AF in patients with HF.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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