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

**Abstract Background/Purpose**

Uric acid is 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 been 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 in accordance with 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 were 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% and a sensitivity of 81%.

**Conclusion** Our study results suggest that serum uric acid levels are 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,2011). P-wave dispersion (PWD) is 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,2017). Several studies have shown that increased PWD can predict atrial fibrillation (AF)( Pérez-Riera,2016). AF and HF commonly coexist. When they exist in conjunction, each condition has a more severe course with an increased risk of mortality(Carlisle,2019). Previous studies have demonstrated that oxidative stress and inflammation can take a significant part in the development of AF in patients with HF(Oikonomou,2019) .

Uric acid, which represents the final product of purine metabolism, is a surrogate marker of inflammation and oxidative stress(Bergamini,2009). Its production is mediated by the xanthine oxidase enzyme. A correlation of increased levels of uric acid with oxidative stress, endothelial dysfunction, and cardiovascular risk has been revealed(Borghi,2018;Shao,2019; Zhao;2012) . Nevertheless, a relationship of increased uric acid levels with the development of AF has been shown in few studies. To the 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.

**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 %) was determined in all of the subjects. 12-lead ECG and blood samples were 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.

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

**ECG examination**

Twelve-lead ECG was 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. The measurement of the P-wave duration was performed in all leads from the start of the P-wave, which was defined as the point at which the initial deflection of the P-wave crossed the isoelectric line, to the ending of the P-wave, which was defined as the point at which the final deflection of the P-wave crossed the isoelectric line. Increased PWD is defined as a PWD of ≥ 40 ms(Dilaveris,1998) . Increased PWD is associated with AF.

Patients in the current research were 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 were performed by means of a 2.5 MHz transducer and a Vivid 7 Dimension® (GE Vingmed Ultrasound AS, N-3190 Horten, Norway) echocardiography device. The measurements were 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 were 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 was used to measure the left atrium size. The left ventricular ejection fraction was computed using the biplane Simpson’s method from apical four-chamber and two-chamber views in accordance with the recommendation of the American Society of Echocardiography 14. The calculation of the systolic pulmonary artery pressure (SPAP) was performed by means of the peak velocity of tricuspid regurgitation and estimated right atrial pressure(Lancelotti,2010) .

**TABLE I**. **Baseline Characteristics of the Patients**

**Variables All patients Group 1 Group 2 p value**

 **(PWD<40ms) (PWD ≥40ms)**

(n=315) (n=201) (n=114)

**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/m2) 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 antagonists(%) 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,±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 0,177Platelet(103 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 ventricule ejection fraction; LA, left atrial diameter; SPAP,systolic pulmonary artery pressure; LVEDD, left ventricule enddiastolic diameter, BUN, blood ure nitrogen; WBC,white blood cell

**RESULTS**

Three hundred fifteen subjects in total (142 females and 173 males) with an average age of 65 ± 12 years were enrolled in the present research. The mean body mass index (BMI) of the patients was 27 ± 4.0 kg/m2. 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 were 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) were 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 are presented in Table 1

**TABLE II. 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 III: Univariate and multivariate analyses for predicting increased PWD**

 Univariate Multivariate

Variable p OR (95% CI) p OR (95% CI)

**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



**AUC=0.83, 95% CI=0.745-0.915, p<0.001**

 **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 were 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 were 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 were 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).

**Discussion**

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,2015) . Oxidative stress and inflammation take a significant part in the development of AF in subjects with HF(Zacharia,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,2011; Nyrnes 2014) .

P-wave dispersion, which is 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 been shown to induce reentry, leading to AF(Pérez-Riera,2016) . A PWD of 40 ms or higher is 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,1998).

Increased PWD has been associated with certain cardiovascular disorders including cardiomyopathies, rheumatic mitral valve stenosis, stroke and hypertension all of which are correlated with a high risk of AF(Dogan,2012; Kocaoglu,2012;Russo,2017; Tsioufis,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,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,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,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, 2019; Huang,2019). Several studies have shown that lowering uric acid levels without altering xanthine oxidase activity does not provide clinical benefit(George,2006; Ogino 2010) . Therefore, xanthine oxidase activity appears to take 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,2005).

In the present study, SPAP was 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,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,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,2013; Tukek 2000).

In the present research, the left atrial diameter was 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,2016;Sarvari,2016;Koide,2002;Tukek,2001).

 P-wave dispersion may be affected by the delay in site-dependent intra-atrial conduction before the onset of left atrial dilatation(Hatam,2014; Gazi, 2015) . However, increased sympathetic activity may affect the propagation of the sinus impulse in subjects with HF. It has also been reported that PWD may be affected by the increased left atrial pressure, diastolic changes, and intraatrial oxidative stress(Gudul,2017).

In the current study, BUN and creatinine levels were 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,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.

**Limitation**

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 were utilized for the purpose of evaluating PWD more accurately(Tukek,2000;Dilaveris 1999). Thirdly, the current research represents a cross-sectional study, and further longitudinal studies are 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 is 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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