P Wave Peak Time for Predicting an Increased Left Atrial Volume Index in Hemodialysis Patients

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Significance of the Study

- The left atrial volume index is a predictor of increased cardiovascular risk in hemodialysis patients.
- This study demonstrates an association between the P wave peak time and the echocardiographically measured left atrial volume index.
- Measuring the P wave peak time duration with an electrocardiogram could help identify high-risk hemodialysis patients with increased left atrial volume indexes.

Keywords

Electrocardiography · Hemodialysis · Left atrial volume index · P wave peak time

Abstract

Objective: An increased left atrial volume index (LAVI) is related to increased mortality in hemodialysis patients. In the present study, we evaluated the association between the LAVI and the P wave peak time (PWPT), a newly introduced electrocardiographic parameter, in hemodialysis patients. Methods: The study population was made up of 79 hemodialysis patients with a mean age of 53 ± 18 years (55.7% were males). These patients were divided into a normal LAVI (≤28 mL/m²) group (n = 45) and an increased LAVI (>28 mL/m²) group (n = 34). The demographic, clinical, laboratory, echocardiographic, and electrocardiographic variables of the groups were compared. Results: The P wave terminal force from lead V1, P wave dispersion and PWPTs obtained from leads V1 and D2 (PWPT D2) were significantly higher in the patients with increased LAVIs. In multivariable analysis, only the PWPT D2 was an independent predictor of an increased LAVI (odds ratio = 1.117, 95% CI = 1.052–1.185, p < 0.001). The receiver-operating characteristic curve analysis showed that the best PWPT D2 cutoff value for predicting an increased LAVI was 60 ms, with a sensitivity of 76.5% and a specificity of 66.7% (area under the curve = 0.736, 95% CI = 0.625–0.829, p < 0.001). Conclusion: This study showed that a prolonged PWPT D2 was independently associated with an increased LAVI in hemodialysis patients. Therefore, measuring the PWPT D2 duration on an electrocardiogram may help define high-risk hemodialysis patients with increased LAVIs.

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Introduction

Left atrial volume (LAV) is closely related to left ventricular (LV) diastolic dysfunction and is affected by the factors associated with LV diastolic filling pressure. LAV is considered to be a biomarker of both the severity and the duration of LV diastolic filling pressure [1]. Enlargement of the left atrium (LA) is associated with poor end points and may be useful for estimating cardiovascular events and death [2, 3]. An increased LAV index (LAVI) has been identified as an important biomarker for chronically increased LV diastolic pressure in hemodialysis patients. Studies have suggested that it could be a predictor of increased cardiovascular risk and mortality in patients with end-stage renal disease (ESRD) [4–6].

Although an echocardiographic assessment of LA enlargement and LV function is standard, it is not always available in clinical practice. However, a 12-lead electrocardiogram (ECG) is a simple, easily accessible and inexpensive tool that can be used to predict the heart cavity volumes and ventricular mass. To date, several of the P wave parameters derived from an ECG, including the P wave terminal force from lead V1 (PTFV1), P wave dispersion (PWD), and the maximum P wave duration (PWD MAX ), have been evaluated for the assessment of LA enlargement and LV diastolic dysfunction in several populations other than ESRD patients [7–11]. Moreover, the P wave peak time (PWPT) has recently been introduced as an echocardiographic parameter. A prolonged PWPT has been found to be related to the increased LV diastolic filling pressure and increased LA pressure because of the imperfect reperfusion in patients with anterior S–T segment elevation myocardial infarction [12].

ESRD is strongly associated with impaired LV diastolic function [13]. However, an echocardiographic assessment is not customary, nor is it easily accessible, for hemodialysis patients. The use of easily accessible diagnostic tools such as an ECG for screening for left atrial enlargement, one of the most important findings of diastolic dysfunction, may facilitate early diagnosis and treatment. Therefore, this study aimed at investigating the relationship between the LAVI and the PWPT in hemodialysis patients.

Subjects and Methods

Study Patients

This study was conducted on patients with ECG-detected sinus rhythms. They were undergoing standard hemodialysis 3 times per week for at least 6 months. Patients with an inadequate echocardiographic image quality, ejection fraction of <50%, significant valvular heart disease, previous history of coronary artery disease and congestive heart failure were excluded. A total of 102 patients who underwent hemodialysis between June 2018 and December 2018 were screened. Nine patients with a history of coronary artery disease, 3 with atrial fibrillation, 5 with inadequate echocardiographic image quality, 4 with significant valvular disease, and 2 with low left ventricular ejection fraction were excluded. The remaining 79 hemodialysis patients constituted the study population.

On the basis of their LAVIs, the patients were classified into a normal LAVI (≤28 mL/m²) group or an increased LAVI (>28 mL/m²) group, and the two groups were compared [2]. On the same day of blood sample collection, echocardiographic examination was performed immediately after ECG recording. All the enrolled patients provided written informed consent, and the study protocol was approved by the institutional review board. The guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were followed [14].

Collection of Demographic, Clinical, and Laboratory Data

Demographic and clinical characteristics were obtained from patient interviews and medical records. Each patient’s height and weight were measured. In addition, routine laboratory tests were conducted by using fasting blood samples taken on the morning of the interdialytic day before the patient underwent the echocardiographic procedure.

Assessment of ECG

Each of the patients underwent a standard 12-lead surface ECG, which was recorded at a speed of 25 mm/s and a voltage of 10 mV/mV. All the ECG printouts were assessed qualitatively for the morphology and quantitatively for the intervals with the ImageJ Java image processing program (imagej.nih.gov/ij/). The ECG assessments were performed by two independent cardiologists blinded to the echocardiographic findings of the patients. In case of disagreement, a final decision was reached by consulting a third cardiologist. The P wave duration measured from the D2 lead (PWD D2 ) was defined as the time from the earliest onset of P wave activity in the D2 lead to the last P wave activity in this lead [15]. The PW D2 was calculated by subtracting the minimum P wave duration (PWD MIN ) from the PWD MAX [16]. The depth of the terminal negative portion of the P wave from lead V1 was multiplied by its duration in order to define the PTFV1 [17]. The duration (ms) from the beginning to the peak of the P wave was measured from lead D2 to define the PWPT from the D2 lead (PWPT D2 ). The PWPT from the V1 lead (PWPT V1) was measured as the interval between the beginning of the P wave to the nadir of the negative deflection in patients with biphasic or pure negative P wave morphology (Fig. 1) [12].

Echocardiographic Assessment

A transthoracic echocardiographic examination of each patient was performed by an experienced cardiologist using an EPIQ 7 ultrasound system for cardiology (Philips Medical Systems, Bothell, WA, USA) on the interdialytic day [18]. Standard echocardiographic imaging was performed, and the measurements were taken in accordance with the American Society of Echocardiography guidelines. Two-dimensional, Doppler, and tissue Doppler echocardiography were used [19, 20]. The LV ejection fraction was cal-
culated with the biplane method (modified Simpson’s rule). LAV measurements were done at the end of systole through the use of the biplane disk summation method, and the LV mass measured with the truncated ellipsoid technique at the end of diastole. The LAV and LV mass were indexed by the body surface area to calculate the LAVI (mL/m²) and the LV mass index (LVMI; g/m²), respectively. The pulsed Doppler sample volume was placed at the tips of the mitral valve leaflets to facilitate the measurement of the peak velocity of the early diastolic transmitial flow (E, cm/s), its deceleration time, and the peak velocity of the late diastolic transmitial flow (A, cm/s). The tissue Doppler sample volume was placed at the lateral corner of the mitral annulus to enable the measurement of the peak mitral annulus velocity (E’, cm/s) by using the apical 4-chamber view. The E/A and E/E’ ratios were calculated, and echocardiographic measurements were averaged over 3 consecutive heartbeats.

**Statistical Analysis**

Statistical analyses were performed with SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA), and a p value < 0.05 was considered to be a statistically significant difference. The demographic, clinical, laboratory, electrocardiographic, and echocardiographic data for the normal LAVI and increased LAVI groups were compared, and the Kolmogorov-Smirnov test was used to analyze the normality of the data distribution. The continuous variables with normal distributions were presented as means and standard deviations, and those without normal distributions were presented as medians (interquartile ranges). The normal LAVI and increased LAVI group comparison was performed with the Student’s t test or the Mann-Whitney U test, as appropriate. The categorical variables were presented as numbers and percentages, and the normal LAVI and increased LAVI group comparison was performed with the χ² or Fisher’s exact test, as appropriate. The correlation analysis of two continuous variables was performed with Pearson’s correlation or Spearman’s rank correlation coefficient for the variables with or without normal distributions, respectively. Two multivariable logistic regression models were developed to determine whether the PWPT parameters were independent predictors of an increased LAVI.

In the first model, multivariable logistic regression analyses were performed with the electrocardiographic variables that showed significant differences in the univariate analysis. In the second model, the PWPT parameters and clinical parameters were found to be associated with the increased LAVI observed in previous studies (age, hypertension, and body mass index [BMI]) [21]. A receiver-operating characteristic (ROC) curve analysis was then performed to determine the best PWPTD2 cutoff value for predicting an increased LAVI. For ease of use in clinical practice, the sensitivity and specificity of the cutoff value of 60 ms (1.5 small squares) were also calculated. The reproducibility of the PWPTD2 and PWPTV1 measurements was tested with the concordance correlation coefficient.

**Results**

The study population comprised 79 hemodialysis patients with a mean age of 53 ± 18 years (55.7% male). They were assigned to one of two groups on the basis of their echocardiographic LAVI measurements. The patients with LAVIs of ≤28 mL/m² were placed in the normal LAVI group (n = 45), and those with LAVIs of > 28 mL/m² were placed in the increased LAVI group (n = 34). Table 1 lists the demographic, clinical, and laboratory characteristics of the patients in each group. There was no statistically significant difference between the groups in terms of age, sex, or BMI. The incidences of hypertension, smoking, diabetes mellitus, and hyperlipidemia were similar for the two groups. In addition, the laboratory measurements, including levels of glucose, blood urea nitrogen, creatinine, sodium, potassium, calcium, phosphorus, hemoglobin, and ferritin, were similar.

Table 1 lists the electrocardiographic and echocardiographic characteristics of the patients. The LV ejection fraction, E, A, E/A ratio, deceleration time, E’, E/E’ ratio, heart rate, QRS duration, bundle branch block frequency, QRS fragmentation frequency, V1 P wave morphology, PWDT2, PWDMIN, and PWDMAX were similar for the groups. However, the LAVI, LVMI, PTFV1, PWDIS, PWPTV1, and PWPTD2 (56 ± 14 vs. 71 ± 20, p < 0.001) were significantly higher in the patients with increased LAVIs than in those with normal LAVIs.

![Fig. 1. Measurement of P wave peak time obtained from D2 and V1 leads.](image-url)
The results of the correlation analysis of the P wave parameters, including the PTFV1, PW\textsubscript{DIS}, PWPT\textsubscript{V1}, and PWPT\textsubscript{D2}, with the echocardiographic parameters, including the LAVI, LVMI, E/A ratio and E/E' ratio are presented in Table 2. The PWPT\textsubscript{V1} and PWPT\textsubscript{D2} exhibited significantly moderate positive correlations with the LAVI. However, the PTFV1 and PW\textsubscript{DIS} exhibited significantly weak positive correlations with the LAVI. The PW\textsubscript{DIS}, PWPT\textsubscript{V1}, and PWPT\textsubscript{D2} exhibited significantly weak positive correlations with the LVMI. However, the
E/A ratio was not correlated with any of the P wave parameters. The E/E’ ratio exhibited a significantly weak positive correlation with the PW DIS only.

The independent predictors of an increased LAVI were identified by multivariable logistic regression analyses through the use of the electrocardiographic variables, including the PTFV1, PW DIS, PWPT V1 and PWPT D2 that showed significant differences in the univariate analysis. The results showed that only the PWPT D2 was an independent predictor of an increased LAVI (odds ratio per 1 ms increase = 1.117, 95% confidence interval [CI] = 1.052–1.185, p < 0.001; Table 3). In addition, the PWPT D2 was found to be an independent predictor of an increased LAVI (odds ratio per 1 ms increase = 1.054, 95% CI = 1.021–1.088, p = 0.001) in the multivariable logistic regression analyses performed with the clinical variables (age, hypertension, and BMI) that were previously shown to be associated with an increased LAVI.

The ROC curve analysis showed that the best PWPT D2 cutoff value for the prediction of an increased LAVI (> 28 mL/m²) prediction (area under the curve = 0.736, 95% confidence interval = 0.625–0.829, p < 0.001). See Table 2. a Comparison of receiver-operating characteristic curves of P wave parameters.

**Table 2.** Correlation analysis of P wave parameters with echocardiographic parameters including LAVI, LVMI, E/A and E/E’ ratios

|                | LAVI, mL/m² | LVMI, g/m² | E/A ratio | E/E’ ratio |
|----------------|-------------|------------|-----------|------------|
| PW DIS, ms     | 0.338       | 0.344      | 0.139     | 0.242      |
| p value        | 0.002       | 0.002      | 0.222     | 0.031      |
| N              | 79          | 79         | 79        | 79         |
| PTFV1, mm × ms |             |            |           |            |
| r value        | 0.316 a     | 0.231 a    | −0.150 a  | 0.090 a    |
| p value        | 0.017       | 0.084      | 0.267     | 0.504      |
| N              | 57          | 57         | 57        | 57         |
| PWPT D2, ms    | 0.586       | 0.307      | −0.019    | 0.120      |
| r value        | <0.001      | 0.006      | 0.871     | 0.294      |
| p value        | 79          | 79         | 79        | 79         |
| PWPT V1, ms    | 0.580       | 0.266      | 0.053     | 0.075      |
| r value        | <0.001      | 0.046      | 0.695     | 0.580      |
| p value        | 57          | 57         | 57        | 57         |

LAVI, left atrial volume index; LVMI, left ventricular mass index; PTFV1, P wave terminal force from lead V1; PW DIS, P wave dispersion; PWPT D2, P wave peak time obtained from D2 lead; PWPT V1, P wave peak time obtained from V1 lead. a Spearman’s correlation analysis was used. Pearson analysis was used for the remaining results.

![Fig. 2. a Receiver-operating characteristic graphic to detect the best cutoff value of PWPT D2 for increased LAVI (>28 mL/m²) prediction (area under the curve = 0.736, 95% confidence interval = 0.625–0.829, p < 0.001). b Comparison of receiver-operating characteristic curves of P wave parameters.](image-url)
An ROC curve comparison analysis was performed on 57 patients (i.e., patients for whom the PTFV1 could be calculated) to compare the P wave parameters. The PWPTD2 was a better predictor (AUC = 0.857, 95% CI = 0.739–0.935) than the PTFV1 (AUC = 0.674, 95% CI = 0.537–0.793; \( p = 0.021 \) and \( p = 0.002 \), respectively; Fig. 2b).

The concordance correlation coefficients of the PWPTD2 and PWPTV1 measurements, performed by the same observer, were 0.991 (95% CI = 0.986–0.994) and 0.992 (95% CI = 0.987–0.995), respectively. The concordance correlation coefficients of the PWPTD2 and PWP-TV1 measurements, performed by two independent observers, were 0.992 (95% CI = 0.988–0.995) and 0.989 (95% CI = 0.981–0.993), respectively.

**Discussion**

This study evaluated the associations between the LAVI and the P wave parameters in hemodialysis patients. Despite the significant differences between the normal LAVI and increased LAVI groups regarding the PTFV1, PWDIS, PWPTV1, and PWPTD2, only a prolonged PWPTD2 was found to be an independent predictor of an increased LAVI. Moreover, the PWPTD2 was correlated with the LAVI.

Incremental increases in the LAVI are an independent predictor of adverse cardiovascular outcomes in patients on hemodialysis. Treatment strategies, such as maintaining a euvoletic state and avoiding overly rapid fluid removal, are efforts to halt the increase in the LAVI in patients on hemodialysis. Given the known prognostic value of the LAVI in hemodialysis patients, it has been an accepted surrogate end point in several studies as treatment target [22, 23]. Therefore, close surveillance of the LAVI of these patients is helpful for monitoring cardiovascular risk and optimizing dialysis therapy.

Atrial stretching resulting from LA pressure overload and LA enlargement could change the electrophysiological properties of the LA myocardium. This can be interpreted on a surface ECG [12, 24, 25]. The P wave parameters derived from an ECG have been shown to be associated and correlated with the LAVI in patient populations other than hemodialysis patients [8, 9]. However, the subanalysis of one study showed that there was no association between the PWDIS and the LA diameter in hemodialysis patients [26]. The measurements were not taken simultaneously in that study; the LA diameter, rather than the LAVI, was used. In the present study, the measurements were taken simultaneously. The PTFV1, PWDIS, PWPTV1, and PWPTD2 were all correlated with the LAVI; however, the correlations were weak for the PTFV1 and PWDIS, and moderate for the PWPTV1 and PWPTD2. After the multivariable logistic regression analysis had been performed, only a prolonged PWPTD2 was found to be an independent predictor of an increased LAVI. Therefore, the PWPTD2 might better reflect the electrophysiological changes resulting from the pressure overload and dilatation of the left atrium.

In previous studies, the LAVI was found to be associated with the diastolic dysfunction grade [1, 27]. Although the E/′E′ ratio was higher in the increased LAVI group, this difference did not reach statistical significance because of the low number of cases in the present study. Moreover, no statistically significant difference was found between the groups regarding the E/A ratio and deceleration time because the increased LAVI group might have contained patients exhibiting all of the stages of diastolic dysfunction. This would have included impaired relaxation, pseudonormalization, and a restrictive filling pattern. Previous studies have reported a correlation between the degree of LA enlargement and the LV mass [1, 27]. The results of the present study confirm those of previous studies: the increased LAVI group exhibited a significantly higher LVMI than the normal LAVI group.

### Table 3. Univariate and multivariable logistic regression analysis of P wave parameters for increased LAVI (>28 mL/m²) prediction

|                      | Univariate analysis |                      | Multivariable analysis |                      |
|----------------------|--------------------|----------------------|------------------------|----------------------|
|                      | odds ratio         | 95% CI               | \( p \) value          | odds ratio         | 95% CI               | \( p \) value          |
| PWDIS, ms            | 1.042              | 1.006–1.080          | 0.02                   | –                    | –                    | –                      |
| PTFV1, mm × ms       | 1.036              | 1.002–1.070          | 0.036                  | –                    | –                    | –                      |
| PWPTD2, ms           | 1.054              | 1.021–1.088          | 0.001                  | 1.117               | 1.052–1.185          | <0.001                 |
| PWPTV1, ms           | 1.060              | 1.013–1.109          | 0.012                  | –                    | –                    | –                      |

CI, confidence interval; LAVI, left atrial volume index; PTFV1, P wave terminal force from lead V1; PWDIS, P wave dispersion; PWPTD2, P wave peak time obtained from D2 lead; PWPTV1, P wave peak time obtained from V1 lead.
This study has several limitations. For example, the sample size was relatively small; therefore, the results need to be validated by larger studies. Because a cross-sectional design was employed, data on the patient prognoses and the temporal changes in the electrocardiographic and echocardiographic parameters are not available. Further prospective studies are needed to assess the clinical effects of these results. The LA volume was measured with two-dimensional echocardiography, which is not as specific and sensitive as cardiac computed tomography or magnetic resonance imaging. In addition, the increased risk of electrolyte imbalance and disturbances in cardiac conduction in ESRD patients might have affected the study results. Moreover, the PWPT D2 cutoff value used to predict an increased LAVI was derived from hemodialysis patients; thus, it cannot be extended to other patient populations.

Conclusion

This study demonstrated that a prolonged PWPT D2 was independently associated with an increased LAVI in hemodialysis patients. This could be a more useful surrogate for an increased LAVI, especially when compared to the effectiveness of the previously identified parameters (PWD\textsubscript{MAX}, PTFV1, and PW\textsubscript{DIS}). For a majority of hemodialysis patients, considerations of the increased likelihood of diastolic dysfunction and the difficulty of access to echocardiography can be addressed by the measurement of the PWPT\textsubscript{D2}, with an ECG to facilitate the identification of the patients with increased LAVIs. Thus, the use of easily obtainable diagnostic tools, such as the PWTP, for screening left atrial enlargement, which is one of the most important findings for diastolic dysfunction, could allow for early diagnosis and treatment.

Statement of Ethics

All the enrolled patients provided written informed consent, and the study protocol was approved by the institutional review board. All study procedures were conducted according to the Declaration of Helsinki.

Disclosure Statement

The authors declare that there is no conflict of interest.

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