Original Article
Association between red cell distribution width and P-wave dispersion in patients with atrial tachyarrhythmia

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Abstract: Although red cell distribution width (RDW) and P-wave dispersion (Pwd) are strong independent predictors of atrial tachyarrhythmia (ATa), the association between these two factors in the occurrence of ATa has hitherto not been reported. We retrospectively analyzed the cases of ATa patients who underwent Holter monitoring at our hospital from October 2013 to August 2014. Clinical data including RDW and color doppler ultrasonography data were collected, and Pwd was calculated from synchronous recording of P-wave intervals of 12-lead electrocardiograms. Patients were categorized into three groups in ascending order of RDW values. Between-group comparisons yielded significant differences in Pwd, left ventricular diastolic diameter (LVDD), and left atrial diameter (LAD; P < 0.05). Pearson correlation analysis revealed that the RDW level positively correlated with the Kleiger grade of atrial arrhythmia (r = 0.280, P < 0.001), Pwd (r = 0.148, P = 0.001), and LAD (r = 0.297, P < 0.001); Pwd positively correlated with the Kleiger grade of atrial arrhythmia (r = 0.257, P < 0.001), aortic root diameter (r = 0.143, P < 0.002), and LAD (r = 0.201, P < 0.001). Binary logistic multiple regression analysis with ATa as the dependent variable revealed that Pwd [odds ratio (OR) = 1.024], RDW [OR = 1.215], and aortic root diameter [OR = 1.030] were significant risk factors for ATa occurrence. This is the first study to establish a correlation between RDW and Pwd in the occurrence of ATa; however, further prospective studies using large cohorts are required to validate the correlation.

Keywords: Atrial arrhythmia, red cell distribution width, P-wave dispersion, left ventricular diastolic diameter, left atrial diameter, aortic root diameter

Introduction
Red cell distribution width (RDW) is a measure of the variation in sizes of peripheral blood erythrocytes, and several studies have shown that RDW can serve as a marker for risk stratification and prognosis of cardiovascular diseases [1, 2]. A recent study demonstrated that elevated RDW values significantly correlated with decreased heart rate variability (HRV) in systolic heart failure patients [3]. Furthermore, elevated RDW was identified as an independent risk factor for new-onset atrial fibrillation (AF) [4].

P-wave dispersion (Pwd) is the difference between the maximum and minimum duration of P-waves as synchronously recorded on 12-lead electrocardiograms; a Pwd > 40 ms indicates the presence of heterogeneous electrical activity in different regions of the atrium that might cause atrial tachyarrhythmias (ATas). Thus, Pwd is a strong predictor of ATAs and especially AF [5-9].

Even though RDW and Pwd are strong independent predictors of ATas, the relationship between these two factors has hitherto not been reported. Therefore, we retrospectively analyzed the relationship between elevated RDW and Pwd in patients with ATa to determine their usefulness as collective risk factors for ATAs.

Materials and methods
Patients
Data of patients with ATa confirmed via Holter monitoring in our hospital from October 2013 to August 2014 were collected. Patients were categorized into grades K1-K6 according to the
Kleiger grading scheme as follows: K1 represents sporadic premature beats < 10 h⁻¹; K2, atrial premature beats > 10 h⁻¹; K3, multifocal atrial premature beats; K4 beats occurring in pairs and in succession; K5, presence of paroxysmal AF, atrial flutters, and atrial tachycardia; and K6, presence of multifocal atrial tachycardia. Patients simultaneously presenting with multiple ATA disorders were categorized into the highest grade. Patients with various types of anemia, rheumatic heart diseases, pulmonary heart diseases, cardiomyopathy, congenital heart diseases, secondary hypertension, persistent AF and atrial flutters, hyperthyroidism, diabetes, and valvular diseases were excluded.

**Clinical and laboratory examination**

Records of clinical and laboratory examination results of the patients who met the inclusion criteria were retrieved and independently entered into a computer database by two cardiologists. Detailed medical history of the patients including age, gender, history of hypertension, and history of patients taking b blockers was obtained. Results of laboratory examination including RDW, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), fasting plasma glucose (FPG), and other clinical indicators were also retrieved. For each patient, 3-ml venous blood had been collected from the median cubital vein in the fasted state. The blood was transferred into a dry test tube for hematology and biochemical analysis. RDW was measured using a fully automated hematology analyzer and various biochemical parameters, such as FPG, TC, TG, HDL-C and LDL-C, were measured using the Hitachi 7170 fully automated high throughput biochemical analyzer. The patients were classified into three groups, namely, Groups A, B, and C, in ascending order of their RDW values according to the grouping scheme adopted by Özcan et al [3].

**Pwd measurement and Holter monitoring**

The 9130P ECG-12-lead type automated electrocardiogram (ECG) machine was used to record 12-lead synchronous ECGs at the sinus heart rate. Cardiac cycles showing steady baseline were selected for measurement of P-wave durations of the respective leads. We continuously measured 3-6 P-wave durations for each lead. The maximum (Pmax) and minimum (Pmin) P-wave intervals for the 12 leads were manually measured, and averages thereof were used for subsequent measurements. Pwd was defined as the difference between Pmax and Pmin, i.e., Pwd = Pmax - Pmin. Holter monitoring data were collected for all the patients during hospital stay. Holter ECGs were recorded according to the group used for comparison in Table 1.

### Table 1. Comparison of baseline data

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=153</td>
<td>n=154</td>
<td>n=153</td>
<td>(ANOVA)</td>
<td></td>
</tr>
<tr>
<td>Male/Female (case)</td>
<td>88/65</td>
<td>90/64</td>
<td>87/66</td>
<td>0.961</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.88±8.652</td>
<td>65.23±8.585</td>
<td>66.82±9.665</td>
<td>0.197</td>
</tr>
<tr>
<td>Application rate of β blocker</td>
<td>68/153</td>
<td>71/154</td>
<td>66/153</td>
<td>0.872</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>137.73±20.47</td>
<td>138.51±25.33</td>
<td>139.92±26.00</td>
<td>0.732</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>81.16±11.11</td>
<td>81.19±12.76</td>
<td>83.74±14.37</td>
<td>0.083</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>6.28±2.89</td>
<td>5.88±2.43</td>
<td>5.77±1.63</td>
<td>0.173</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.41±0.65</td>
<td>1.37±0.91</td>
<td>1.45±0.94</td>
<td>0.695</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.21±0.31</td>
<td>1.26±0.44</td>
<td>1.22±0.45</td>
<td>0.074</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.57±0.72</td>
<td>2.64±0.89</td>
<td>2.67±0.87</td>
<td>0.156</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.59±1.16</td>
<td>4.62±1.32</td>
<td>4.64±1.48</td>
<td>0.528</td>
</tr>
<tr>
<td>Aortic root diameter (mm)</td>
<td>31.01±3.09</td>
<td>31.28±3.08</td>
<td>31.54±3.37</td>
<td>0.051</td>
</tr>
<tr>
<td>LVDD (mm)</td>
<td>46.25±4.56</td>
<td>46.88±4.78</td>
<td>47.89±5.93</td>
<td>0.019</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>36.26±4.67</td>
<td>39.29±4.88</td>
<td>41.08±6.17</td>
<td>0.00012</td>
</tr>
<tr>
<td>Average heart beat (bmp)</td>
<td>67.41±7.94</td>
<td>65.39±7.34</td>
<td>68.48±9.39</td>
<td>0.088</td>
</tr>
<tr>
<td>Pwd (ms)</td>
<td>30.48±14.29</td>
<td>34.57±17.39</td>
<td>39.70±17.39</td>
<td>0.00035</td>
</tr>
</tbody>
</table>
using the MDS 300-4A Type Holter (DMS, USA). The ECGs were then analyzed by a dedicated cardiologist using the Cardio Scan Luxury Holter ECG analysis software, Advanced Analysis Version (DM Software Inc., Beijing). Artifacts and interferences were eliminated, and the Pwd values were calculated.

The analysis process described above strictly follows the single-blind principal, i.e., the data analyzer was unaware of the specific grouping condition of the patient, and the clinicians did not know the data analysis calculations.

**Color doppler ultrasonography**

Patients were asked to lie in the left-lateral position and breathe calmly. The left ventricular diastolic diameter (LVDD) and the left atrial diameter (LAD) were measured in the regular manner from the left edge view of the sternum and from the apical four-chamber view. The aortic root diameter, i.e., the distance from the inner echo edge of the front-wall to the rear-wall of the aortic root, was measured in the regular manner from the aortic long-axis view besides the sternum.

**Statistical analysis**

Numerical data are represented as means ± the standard deviation, and the categorical variables are represented as frequencies or percentages. The independent-sample t test was used for comparisons between two groups, and analysis of variance was used for comparisons between more than two groups of data. Fischer’s least significant difference (LSD) test and the Student-Newman-Keuls test were used for between-group comparisons. Pearson correlation analysis was performed to determine the correlations between any two indicators, including RDW and Pwd. Binary logistic multiple regression analysis was performed with ATa (considered to be 0 for Kleiger grades K1-K3 and 1 for grades K4-K6) as the dependent variable to determine the independent risk factors for ATa. All statistical analyses were conducted using the SPSS20.0 software. A P-value of < 0.05 was considered statistically significant.

**Results**

**Comparison of baseline data**

Patients were divided into Group A, B, and C in ascending order of RDW values. No significant differences were observed between any of the three groups in terms of gender, age, blood pressure levels, plasma glucose levels, blood lipid profile, average heart rate, and aortic root diameter (P > 0.05). However, significant differences existed between the three groups in terms of RDW values, Pwd, LVDD, and LAD (P < 0.05 for all parameters). Moreover, Pwd, LVDD, and LAD increased with increase in RDW values (Table 1).

**Correlation between RWD, Pwd, and ATa**

After the confounding factors had been eliminated, correlation analysis was conducted to allow pair-wise comparison of all the variables using Pearson correlation analysis. RDW values were positively correlated with the Kleiger grade of ATa (r = 0.280, P < 0.001), Pwd (r = 0.148, P = 0.001), and LAD (r = 0.297, P < 0.001). Pwd values were also positively correlated with the Kleiger grade of ATa (r = 0.257, P < 0.001), aortic root diameter (r = 0.143, P = 0.002), and LAD (r = 0.201, P < 0.001).

**Independent risk factors for ATa**

In order to identify the independent risk factors for ATa, binary logistic multiple regression analysis was conducted. ATa (considered to be 0 for grades K1-K3 and 1 for grades K4-K6) was the dependent variable. Gender (female = 0, male = 1), hypertension (no = 0, yes = 1), age, plasma glucose, total cholesterol, RDW, TC, HDL-C, LDL-C, triglycerides (TG), LVDD, aortic root diameter, LAD, average heart beat, and Pwd were considered as independent variables. LAD and LVDD were not introduced into the regression equation. Pwd (OR = 1.024), RDW (OR = 1.215), and aortic root diameter (OR = 1.030) were found to be independent risk factors for ATa (Table 2).

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**Table 2. Binary logistic multiple regression analysis of critical risk factors for atrial tachyarrhythmia**

<table>
<thead>
<tr>
<th>Model</th>
<th>B</th>
<th>SE</th>
<th>P value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pwd</td>
<td>0.024</td>
<td>0.007</td>
<td>0.001</td>
<td>1.024</td>
<td>1.009-1.039</td>
</tr>
<tr>
<td>RDW</td>
<td>0.194</td>
<td>0.095</td>
<td>0.041</td>
<td>1.215</td>
<td>1.008-1.464</td>
</tr>
<tr>
<td>Aortic root diameter</td>
<td>0.122</td>
<td>0.047</td>
<td>0.010</td>
<td>1.130</td>
<td>1.030-1.239</td>
</tr>
</tbody>
</table>
Risk factors for atrial tachyarrhythmia

Discussion

Elevated RDW values are mainly attributed to inadequate production of erythrocytes due to deficiency of Fe, vitamin B12, or folic acid; increased erythrocyte damage; and chronic inflammation. A recent study showed that elevated RWD levels are associated with cardiovascular diseases. Felker et al. first reported that an elevated RDW value is a strong predictor of poor prognosis in cardiovascular disease patients and an independent predictor of mortality in patients with chronic heart failure [10]. Thereafter, several studies confirmed the association of RDW and coronary artery diseases, and it was identified as a valuable indicator for risk stratification and prognosis evaluation of coronary artery diseases [11-13]. Adamsson Eryd S et al. divided a cohort of 27124 healthy individuals without heart failure, myocardial infarction, apoplexy, or AF into four groups in ascending order of their RDW values and followed them up for an average of 13.6 years; morbidity rate because of AF in the group with the highest RDW values was 1.33 times that in the group with the lowest RDW level (95% CI = 1.16-1.53). Moreover, high RDW values significantly correlated with AF-associated first-admission rate; thus, RDW could be a useful predictor of morbidity rate associated with AF [4]. Consistent with the above findings, Ertas et al. found that RDW can predict AF occurrence patients without a history of AF who have undergone coronary artery bypass grafting [14]. A recent study by Kurt et al. shows that for patients with nonvalvular AF, RDW value is positively correlated with the CHA\textsuperscript{2}RDS\textsuperscript{2}-VASc score and that RDW is an independent predictor of CHA\textsuperscript{2}RDS\textsuperscript{2}-VASc scores [15]. Furthermore, RDW is also a predictor of thromboembolism risk in patients with AF. Thus, several studies have confirmed that the RDW value is correlated with occurrence of AF.

In our retrospective analysis of 460 patients with ATa, RDW values were found to be significantly different between the three groups (P < 0.05), and LVDD and LVD were found to increase with increase in the RDW values. Moreover, the RDW value was found to be positively correlated with the Kleiger grade and LAD, and elevated RDW was found to be a critical risk factor for ATA. Pwd is an indicator of site-specific heterogeneous electrical activity in the atrium, and it acts as an important electrophysiological tool for determining the occurrence of ATas and especially AF. Because of the lack of a well-coordinated conduction system within the atrial muscles, extreme asynchronism between the left and right atria, insufficient blood supply, significant anisotropy in myoelectric activity, and thin wall thickness (which tends to cause expansion). Thus, the small cell size and chaotic arrangement of muscle fibers of the atria cause an imbalance in the electrophysiology and spatial dispersion of these muscles in the excited state. The atrial muscles are abundantly connected with autonomic nerve endings that significantly affect their electrophysiological properties. Excitation of the sympathetic nerves can increase cardiac muscle automaticity, trigger electrophysiological activity, and thereby increase the occurrence of ATas. Moreover, excitation of the parasympathetic nerves tends to increase reentry of electrical activity in the atria. Impaired function of the autonomic nerves exacerbates the heterogeneity in electrical activity of the atrial muscles and causes significant differences in spatial vectors and dispersion. On a 12-lead electrocardiogram, these changes are reflected as significant differences in the durations of P-waves of various leads, thus causing an increase in Pwd. In our study, Pwd was positively correlated with the Kleiger grade, aortic root diameter, and LAD; moreover, multiple regression analysis with ATa as the dependent variable identified Pwd as a critical risk factor for ATa. These results are consistent with the the previous research conclusions [16-18]. Our results demonstrated that Pwd is positively correlated with the RDW value for all the three groups. This finding indicates that elevated RDW levels contribute to the occurrence of ATas possibly via affecting Pwd. Thus, this is the first study to establish a correlation between RDW level and Pwd in the occurrence of AF.

The potential mechanism that causes ATa via alteration of RDW levels and Pwd is hitherto unknown. Bogdan showed that increased concentrations of free radicals can accelerate the dissolution of erythrocytes, and the diminished erythrocyte number acts as a trigger for hematopoiesis, thereby causing an increase in RDW levels [19]. Both inflammation and oxidative...
stress can elevate RDW levels [20, 21]. Some researchers hypothesize that long-term activation of the neuroendocrine system may also inhibit medullary hematopoiesis to cause an increase in RDW levels. Özcan et al recently showed that in 180 patients with systolic heart failure who underwent 24-h Holter monitoring, the RDW levels were independently and negatively correlated with all the HRV parameters (i.e., standard deviation of all normal RR intervals, standard deviation of the averages of RR intervals in all 5-min segments, and root-mean square of difference of successive RR intervals) [3]. This finding indicates that elevated RDW levels in patients with heart failure are associated with impairment of autonomic nerves. Activation of the neuroendocrine system or inflammation cause structural reconstruction of the atria, and the left atrium expands to promote occurrence of ATa. This hypothesis is supported by the fact that LAD was positively correlated with both RDW and Pwd in our study. A study by Simsek et al also found that Pwd increases in patients with iron deficiency or anemia, which are disorders characterized by elevated RDW levels; however, actual RDW levels were not measured in this study to confirm the hypothesis that RDW and Pwd are directly correlated in such conditions [22].

Our study had certain limitations. Because it was a retrospective analysis and multiple RDW values could not be obtained, some variability could exist in the Pwd measurements. This is the first study to establish a correlation between RDW and Pwd in the occurrence of ATAs, further clinical studies using large cohorts and a prospective design are required to validate the correlation. Moreover, mechanistic studies should also be employed to elucidate the mechanism by which this association affects ATa pathophysiology.

Disclosure of conflict of interest

None.

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References


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