Analysis of relationship between P wave dispersion and diagnosis of pulmonary arterial hypertension and risk stratification

Jun Luo  
The Second Xiangya Hospital of Central South University

Jingjie Sun  
The Second Xiangya Hospital of Central South University

Li Xu  
The Affiliated Cancer Hospital of Xiangya School of medicine, Central South University

Jingyuan Chen  
The Second Xiangya Hospital of Central South University

Yusi Chen  
The Second Xiangya Hospital of Central South University

Wenjie Chen  
The Second Xiangya Hospital of Central South University

Haihua Qiu  
The Second Xiangya Hospital of Central South University

Xiaojin Luo  
The Second Xiangya Hospital of Central South University

Sisi Chen  
The Second Xiangya Hospital of Central South University

Jiang Li (✉ lijiangcs@csu.edu.cn)  
The Second Xiangya Hospital of Central South University

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Abstract

Objectives: The aim of this study was to measure the P-wave dispersion (PWD) in the ECG of patients with pulmonary arterial hypertension (PAH).

Methods: A total of 103 PAH patients were collected, including 55 patients related with CHD and 44 patients with IPAH. In addition, 30 CHD patients without PAH (nPAH-CHD group) and 30 healthy controls (HCG group) were collected as control. Patients in the PAH group were categorized into the low-risk group (30 cases), moderate-risk group (53 cases) and high-risk group (20 cases), followed by comparison of PWD difference between groups. The ROC curve was used to evaluate the diagnostic efficacy of PWD on PAH-CHD and IPAH.

Results: The levels of PWD and Pmax in PAH-CHD and IPAH group were significantly higher than those in nPAH-CHD and HCG group (P<0.05). PWD level was positively correlated with RVD, RAS, mPAP, PVR (r=0.407, 0.470, 0.477, 0.423, P<0.001), and was negatively correlated with TAPSE level (r =-0.551, P<0.001). After risk quantification in 103 PAH patients, we found that PWD was significantly different among the low-risk, moderate-risk and high-risk groups (43.89 ± 9.91 vs. 51.29 ± 6.61, 62.15 ± 10.44, P<0.001). CHD-PAH and IPAH were identified by PWD with a cut off value of 41.5ms (P< 0.001), and a cut off value of 41.45ms (P< 0.001), respectively.

Conclusion: PWD might be an effective ECG indicator for PAH, which might be used as a relatively economical and easily accessible indicator for PAH patients to assist in early diagnosis, disease severity assessment and prognosis evaluation.

Introduction

Pulmonary arterial hypertension (PAH) is a disease caused by many reasons. Small pulmonary artery stenosis or occlusion is the main pathophysiological change, which limits the blood flow through the pulmonary artery circulation, leading to an increase in pulmonary vascular resistance (PVR), and eventually leading to right heart failure (HF)[1]. PAH is defined as mean pulmonary arterial pressure (MPAP) ≥ 25 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15mmHg, and PVR ≤ 3woods[2]. PAH changes the homogeneity of ventricular repolarization and atrial conduction by regulating autonomic nerve activity, delaying cardiac repolarization, and right ventricular myocardial ischemia, thereby increasing the probability of various arrhythmias. These arrhythmias can be easily shown with noninvasive surface 12-lead electrocardiography (ECG)[3].

The heterogeneity of atrial conduction can be considered as the change of P-wave duration (PWD) between surface ECG leads in different orientations. PWD is the difference between the maximum and minimum P-wave durations in different ECG leads. PWD duration was used to assess the even distribution of sinus impulses. In addition, they are used to assess intra-atrial and interatrial conduction time, and are currently used primarily in patients with paroxysmal atrial fibrillation (AF)[4]. However, the use of PWD in PAH patients is currently limited[5].

The aim of this study was to measure the PWD in the ECG of patients with PAH, to explore the correlation of PWD levels with diagnosis, disease assessment and risk stratification among PAH patients, and to evaluate the feasibility and clinical value of PWD as a characteristic indicator for PAH patients.

Methods

2.1 Patient Population and Study Design

The inclusion criteria were: 1) according to the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines, the haemodynamic definition of PAH relies on a mPAP≥25 mmHg at rest, PAWP≤15 mm Hg and PVR >3 Woods[2]; 2) patients with congenital heart disease(CHD) associated with PAH and idiopathic PAH(IPAH). The exclusion criteria were: 1) PAH except CHD-PAH and IPAH; 2) combined with hypertension, coronary artery disease, hypertrophic cardiomyopathy, rheumatic mitral stenosis, renal failure, hyperthyroidism, obstructive sleep apnea syndrome and other diseases; 3) combined with obvious arrhythmias: including atrial fibrillation, preexcitation syndrome, supraventricular tachycardia, atrioventricular block, left bundle branch block and pacemaker rhythm; 4) patients with serum electrolyte imbalance and receiving antiarrhythmic medications.

From January 2016 to October 2019, a total of 103 patients fulfilling the inclusion criteria were evaluated; 59 patients as PAH-CHD group and 44 patients as IPAH Group. 30 patients with CHD but no PAH(nPAH-CHD group) and 30 healthy control groups(HCG) were enrolled as a Control group. They were selected from The Second Xiangya Hospital of Central South University.

All patients signed informed consent to the study according to a protocol approved by the Ethical Committee of The Second Xiangya Hospital of Central South University.

We collected the basic clinical information of these patients, including sex, age, physical examination, echocardiography, six-minute walk test distance (6MWD), hemodynamic parameters, and blood tests for biochemical markers associated with clinical severity.

2.2 Echocardiographic evaluation
Echocardiography was performed by two experienced cardiologists at rest. The patient was in the left lying position, using commercial echocardiography equipment (video 7, General Electric, Milwaukee, WI, USA) and 3-MHz transducers. Transesophageal and transthoracic echocardiography was performed within 24 hours before operation. The pulmonary artery systolic pressure (SPAP) was calculated from the tricuspid regurgitation velocity of parasternal short axis and apical four chamber view using Bernoulli equation, and statistical analysis was performed. A SPAP< below 30 mm Hg is defined as normal. PAH was divided into mild (SPAP=30-44 mmHg), moderate (SPAP=45-59 mmHg), and severe (SPAP≥60 mmHg) based on SPAP. All parameters were measured separately for three times and averaged. The coefficients of intra-observer and inter-observer variation of echocardiographic parameters were less than 5% and were not significant.

2.3 Right heart catheterization

Patients were diagnosed by RHC according to criteria: mPAP≥25 mmHg and PVR 3 WU at rest in the presence of a normal PCWP (≤15 mmHg). Heart rate and systemic blood pressure were measured just before RHC. The catheter was passed through the femoral vein sheath and RA, RV, pulmonary artery, and PCWP were measured. Cardiac output (CO) was measured by Fick method, using oxygen consumption. Cardiac index (CI) was calculated as follows:

$$CI (l/min/m^2) = \frac{CO (l/min)}{body surface (m^2)}$$

PVR was calculated as:

$$PVR (WU) = \frac{mPAP (mmHg) - PCWP}{CO (l/min)}$$

All parameters are calculated as the average of three different measurements. After obtaining baseline hemodynamics, acute vascular response tests were performed with inhaled nitric oxide or iloprost.

2.4 ECG measurements

The 12-lead synchronous electrocardiogram recording method was adopted. The paper walking speed was 25mm/s and the amplitude was 10mm/mV. Use Cardio Calipers version 3.3 software to measure PWD of electrocardiogram. The intersection of the starting point of P wave and equipotential line is taken as the starting point of P wave, the intersection of the ending point of P wave and equipotential line is taken as the ending point of P wave. The maximum value is the maximum P-wave time limit (Pmax), the minimum is the minimum P-wave time limit (Pmin), and the difference between them is p-wave dispersion (PWD). Each lead continuously measured three P wave time limits and took the average value. 30 patients were randomly selected for the PWD repeatability study. The same measurer measured PWD with the same method at different times to test the repeatability of this method. PWD measured separately for three times and averaged. The coefficients of intra-observer and inter-observer variation of echocardiographic parameters were less than 5% and were not significant.

2.5 Risk assessment of PAH

Patients were categorized as 'Low risk', 'Intermediate risk', or 'High risk' on the basis of cut-off values for NT-proBNP, mean right atrial pressure, pericardial effusion, right atrial area, cardiac index, 6 minutes walking distance, mixed venous oxygen saturation, cardiac function, and defined in the risk assessment instrument from the 2015 ESC/ERS guidelines (Table 1). Each variable was graded from 1 to 3 where 1 = 'Low risk', 2 = 'Intermediate risk', and 3 = 'High risk'. Divide the sum of all grades by the number of variables available per patient to get the average grade. The average score was rounded to an integer to define the risk group of the patient[6]. In addition, according to the 2015 ESC/ERS guidelines, patients with PAH(CHD-PAH and IPAH) are divided into low-risk groups (30 patients), medium-risk groups (53 patients), and high-risk groups (20 patients). Risk stratification was assessed at baseline and at follow-up.

Table 1 Variables and their thresholds in the risk assessment tool included in the ESC/ERS 2015 Guidelines for the Diagnosis and Treatment of pulmonary hypertension.
Determinants of prognosis

<table>
<thead>
<tr>
<th>WHO functional class</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD m</td>
<td>&gt;440</td>
<td>165~440</td>
<td>&lt;165</td>
</tr>
<tr>
<td>NT-proBNP(ng/L)</td>
<td>&lt;300</td>
<td>300~1400</td>
<td>&gt;1400</td>
</tr>
<tr>
<td>pericardial effusion</td>
<td>No</td>
<td>No or minimal</td>
<td>exist</td>
</tr>
<tr>
<td>right atrium area(cm²)</td>
<td>&lt;18</td>
<td>18~26</td>
<td>&gt;26</td>
</tr>
<tr>
<td>RAP(mmHg)</td>
<td>&lt;8</td>
<td>8~14</td>
<td>&gt;14</td>
</tr>
<tr>
<td>SvO₂(%)</td>
<td>&gt;65</td>
<td>60~65</td>
<td>&lt;60</td>
</tr>
<tr>
<td>CI(L/min/m²)</td>
<td>≥2.5</td>
<td>2.1~2.4</td>
<td>≤2.0</td>
</tr>
</tbody>
</table>

Use the risk assessment tools in the 2015 ESC/ERS pH diagnosis and treatment guidelines. It is recommended to achieve a low-risk level as the treatment goal.[2]

6MWD, 6-minute walking distance; CI, cardiac index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RA, right atrium; RAP, right atrial pressure; SvO₂, mixed venous oxygen saturation; WHO, World Health Organization.

2.6 Statistical Analysis

The SPSS 19.0 computer program (SPSS, Chicago, IL, USA) was used for the statistical analysis. The data is shown as the mean ± standard deviation of normally distributed variables, while the variables without a normal distribution are shown as the median, minimum, and maximum. The repeatability of the two groups of data with normal distribution is studied by paired sample t-test, and the comparison between the two sample groups is conducted by independent sample t-test. The nonparametric rank sum test (Mann Whitney U method) is used for the comparison between groups with nonnormal distribution. The adoption rate or constituent ratio (%) of counting data is expressed, and the comparison of rates is adopted χ² test, Pearson correlation coefficient is used for correlation analysis between variables that conform to normal distribution, and Spearman correlation coefficient is used for correlation analysis between variables that do not conform to normal distribution.

A p value lower than 0.05 was considered to be statistically significant. The receiver operating characteristic curve (ROC curve) was used to evaluate the diagnostic efficacy of PWD for the occurrence of PAH-CHD and IPAH (including sensitivity, specificity, positive predictive value, negative predictive value, Youden index, accuracy), and the test level α=0.05.

2.7. Ethical considerations

The study protocol was approved by the Ethics Committee for Human Study, The Second Xiangya Hospital, Central South University. The study was performed in accordance with the Declaration of Helsinki.

Results

3.1 General clinical and laboratory data

Demographic data for the study population are presented in Table 1. There were no significant differences in baseline characteristics between groups in terms of age, gender, body mass index, heart rate, diastolic blood pressure. The height, weight, systolic blood pressure were significantly depressed in patients with PAH and PAH-CHD compared to HCG (P<0.05). The height, weight, systolic blood pressure were significantly depressed in patients with PAH and PAH-CHD group compared to HCG (P<0.05). The height and systolic blood pressure were significantly depressed in patients with IPAH group compared to HCG (P<0.05). The systolic blood pressure level in the PAH group was lower than that in the nPAH-CHD group (P<0.05). The mean arterial pressure level in the PAH-CHD group was lower than that in the nPAH-CHD group (P<0.05).

The haemoglobin, hematocrit, red cell distribution width uric acid(RWD-CV), serum total bilirubin(TBIL), uric acid(UA) and N-terminal pro-brain natriuretic peptide(NP-BNP) levels were significantly elevated in patients with PAH, PAH-CHD, IPAH group compared to HCG (P<0.05). The haemoglobin, hematocrit, RWD-CV, UA and NT-proBNP levels were significantly elevated in patients with PAH, PAH-CHD, IPAH group compared to nPAH-CHD group (P<0.05). Compared with nPAH-CHD patients, the level of TBIL in IPAH patients was significantly higher (P<0.05). The TBIL levels were significantly elevated in patients with nPAH-CHD compared to HCG (P<0.05). Compared with nPAH-CHD group, the levels of TBIL, NT proBNP and UA in IPAH patients were significantly higher (P<0.05) (Table 1).

Table 1 Baseline clinical characteristics
### Table 2 Hemodynamic parameters of study groups ( mean ± SD)

<table>
<thead>
<tr>
<th>General Data</th>
<th>PAH group (n=103)</th>
<th>PAH-CHD group (n=59)</th>
<th>IPAH group (n=44)</th>
<th>nPAH-CHD group (n=30)</th>
<th>HCG group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shunt type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial septal defect, n (%)</td>
<td>32/71</td>
<td>18/41</td>
<td>14/30</td>
<td>7/23</td>
<td>9/21</td>
</tr>
<tr>
<td>Ventricular septal defect, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patent ductus arteriosus, n (%)</td>
<td>1(2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atroventricular septal defect, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>32/71</td>
<td>18/41</td>
<td>14/30</td>
<td>7/23</td>
<td>9/21</td>
</tr>
<tr>
<td>Age (year)</td>
<td>36.13±10.84</td>
<td>33.90±9.19</td>
<td>35.93±12.27</td>
<td>36.27±9.74</td>
<td>35.43±9.94</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.59±7.99</td>
<td>1.58±7.95</td>
<td>1.59±8.10</td>
<td>1.60±7.61</td>
<td>1.63±6.31</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>54.00±10.74</td>
<td>53.43±10.32</td>
<td>54.77±11.35</td>
<td>54.57±9.09</td>
<td>58.59±9.77</td>
</tr>
<tr>
<td>BMI Kg/m²</td>
<td>21.18±3.25</td>
<td>20.83±2.96</td>
<td>21.66±3.58</td>
<td>21.35±3.22</td>
<td>21.94±2.75</td>
</tr>
<tr>
<td>HR (times/min)</td>
<td>85.23±14.63</td>
<td>84.22±15.38</td>
<td>86.59±13.62</td>
<td>84.03±13.12</td>
<td>81.37±9.48</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>111.36±13.46</td>
<td>111.95±12.47</td>
<td>110.57±14.80</td>
<td>116.07±10.42</td>
<td>118.07±13.04</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74.52±11.08</td>
<td>72.83±11.83</td>
<td>76.80±9.64</td>
<td>76.80±7.83</td>
<td>75.40±9.38</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>86.80±10.56</td>
<td>85.87±10.85</td>
<td>88.05±10.15</td>
<td>89.89±7.59</td>
<td>89.63±9.33</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>144.38±23.03</td>
<td>142.64±24.16</td>
<td>146.70±21.49</td>
<td>129.3±18.93</td>
<td>128.67±15.86</td>
</tr>
<tr>
<td>HCT (%)*</td>
<td>43.3(39.9,80)</td>
<td>42.40(39.3,45.6)</td>
<td>44.1(40.9,48.7)</td>
<td>39.4(37.0,41.6)</td>
<td>38.8(35.7,42.8)</td>
</tr>
<tr>
<td>RDW-CV (%)</td>
<td>14.23±2.33</td>
<td>14.00±2.43</td>
<td>13.85±2.20</td>
<td>12.98±1.38</td>
<td>13.00±1.15</td>
</tr>
<tr>
<td>TBIL (umol/L)*</td>
<td>14.4(10.1,19.1)</td>
<td>12.9(9.3,15.7)</td>
<td>18.3(12.0,26.6)</td>
<td>12.4(9.5,15.0)</td>
<td>8.95(7.4,12.7)</td>
</tr>
<tr>
<td>UA (umol/L)</td>
<td>397.32±124.65</td>
<td>366.44±106.57</td>
<td>438.73±135.93</td>
<td>279.5±79.2</td>
<td>306.22±101.82</td>
</tr>
<tr>
<td>NT-ProBNP (pg/mL)*</td>
<td>989.9(302.86,2831.4)</td>
<td>685.9(178.1,1258.2)</td>
<td>2165.9(954.9,3938.1)</td>
<td>139.52(25.13,239.79)</td>
<td>45.7(14.5,71.69)</td>
</tr>
</tbody>
</table>

Values are mean±SD or numbers (percentages), * means the variable does not conform to a normal distribution. A p value 0.05 was considered statistically significant. BMI: Body Mass Index HR: Heart Rate SBP: systolic pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; Hb: hemoglobin; HCT: hematocrit; RDW-CV: Red blood cell distribution width-CV; TBIL: total bilirubin; UA: Uric acid; NT-proBNP: N-terminal brain natriuretic peptide precursor. #, compared to HCG group; &, compared to nPAH-CHD group; ▲, compared to PAH-CHD group.

#### 3.2 Hemodynamic data

No significant difference was observed in the aortic dimension (AoD) among any two groups (P>0.05, See Table 2). The right ventricular diastolic diameter (RVD), right atrial systolic diameter (RAS), and pulmonary artery diameter (PA) were higher in PAH and nPAH-CHD group than HCG (P<0.05). The tricuspid ring systolic displacement (TAPSE) in PAH and nPAH-CHD group was lower than HCG (P<0.05). The RVD, PA and RAS were higher in PAH patients than nPAH-CHD (P<0.05, Table 2).
### Hemodynamic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PAH group (n=103)</th>
<th>PAH-CHD group (n=59)</th>
<th>IPAH group (n=44)</th>
<th>nPAH-CHD group (n=30)</th>
<th>HCG group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDd(mm)</td>
<td>41.8±10.18</td>
<td>45.37±10.54</td>
<td>37.11±7.48</td>
<td>40.83±3.57</td>
<td>43.63±3.62</td>
</tr>
<tr>
<td>LAS(mm)</td>
<td>35.6±9.66*</td>
<td>39.42±8.84*</td>
<td>30.57±8.37</td>
<td>30.02±4.30</td>
<td>27.93±3.02</td>
</tr>
<tr>
<td>RVD(mm)</td>
<td>45.40±10.03</td>
<td>43.19±10.34</td>
<td>48.36±8.85</td>
<td>38.23±6.78</td>
<td>28.40±3.53</td>
</tr>
<tr>
<td>RAS(mm)</td>
<td>41.23±8.68*</td>
<td>37.92±7.16*</td>
<td>46.68±8.62</td>
<td>37.70±7.39</td>
<td>27.17±3.79</td>
</tr>
<tr>
<td>AO(mm)</td>
<td>27.39±10.12</td>
<td>28.46±13.01</td>
<td>25.95±3.26</td>
<td>25.90±3.19</td>
<td>26.10±2.63</td>
</tr>
<tr>
<td>PA(mm)</td>
<td>32.72±7.09</td>
<td>35.29±7.69</td>
<td>29.27±4.30</td>
<td>23.97±3.59</td>
<td>20.17±1.95</td>
</tr>
<tr>
<td>LVEF(%)</td>
<td>60.29±8.43</td>
<td>58.94±9.31</td>
<td>62.09±6.78</td>
<td>64.33±3.61</td>
<td>63.33±3.31</td>
</tr>
<tr>
<td>TAPSE(mm)</td>
<td>12.08±4.01</td>
<td>13.20±4.01</td>
<td>10.81±3.61</td>
<td>21.27±1.96</td>
<td>22.10±1.37</td>
</tr>
<tr>
<td>mRAP(mmHg)*</td>
<td>10.00(7.00,13.00)</td>
<td>8.00(6.00,11.00)</td>
<td>11.50(8.00,16.00)</td>
<td>7.00(4.00,10.00)</td>
<td>NA</td>
</tr>
<tr>
<td>mRVP(mmHg)</td>
<td>40.78±10.18</td>
<td>39.86±10.91</td>
<td>42.00±9.08</td>
<td>16.20±4.31</td>
<td>NA</td>
</tr>
<tr>
<td>mPAP(mmHg)</td>
<td>59.26±15.19</td>
<td>58.90±17.18</td>
<td>59.75±12.19</td>
<td>19.17±3.21</td>
<td>NA</td>
</tr>
<tr>
<td>PCWP</td>
<td>8.23±1.51</td>
<td>7.92±1.32</td>
<td>7.89±1.15</td>
<td>8.14±1.24</td>
<td>NA</td>
</tr>
<tr>
<td>Qs(L/min)</td>
<td>3.55±1.25</td>
<td>3.82±1.12</td>
<td>3.18±1.32</td>
<td>4.24±1.35</td>
<td>NA</td>
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<tr>
<td>Qp/Qs*</td>
<td>1.00(1.00,1.78)</td>
<td>1.61(1.20,2.41)</td>
<td>1</td>
<td>1.86(1.54,3.03)</td>
<td>NA</td>
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<tr>
<td>SVR(wood)</td>
<td>27.72±10.76</td>
<td>24.51±8.10</td>
<td>32.03±12.37</td>
<td>23.44±7.80</td>
<td>NA</td>
</tr>
<tr>
<td>PVR(wood)*</td>
<td>14.50(7.50,21.37)</td>
<td>8.60(5.50,17.90)</td>
<td>19.86(14.47,29.49)</td>
<td>2.04(1.61,2.54)</td>
<td>NA</td>
</tr>
<tr>
<td>PVR/SVR*</td>
<td>0.58(0.33,0.77)</td>
<td>0.36(0.25,0.76)</td>
<td>0.67(0.58,0.77)</td>
<td>0.11(0.07,0.14)</td>
<td>NA</td>
</tr>
<tr>
<td>SvO2(%)</td>
<td>63.52±10.18</td>
<td>65.25±9.90</td>
<td>61.21±10.20</td>
<td>69.03±7.18</td>
<td>NA</td>
</tr>
<tr>
<td>CI(L/min/m²)</td>
<td>2.72(1.86,4.53)</td>
<td>3.68(2.60,6.07)</td>
<td>1.92(1.49,2.42)</td>
<td>6.21(4.98,7.61)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are mean±SD or numbers (percentages), * means the variable does not conform to a normal distribution. A p value 0.05 was considered statistically significant. LVEDd: left ventricular end-diastolic diameter; LAS left atrial systolic diameter; RVD: right ventricular diastolic diameter; RAS: right atrial systolic diameter; AO: aortic diameter; PA: main pulmonary artery diameter; LVEF: left ventricular ejection fraction TAPSE: systolic displacement of the tricuspid annulus; mRAP: right atrial mean pressure; mRVP: right ventricular mean pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; Qp: pulmonary blood flow; Qs: systemic blood flow; Qp/Qs pulmonary blood flow/systemic blood flow; SVR: systemic resistance; PVR: pulmonary circulation resistance; PVR/SVR: pulmonary circulation resistance / systemic resistance; SvO2: mixed venous oxygen saturation; CI: cardiac index; NA: unusable data. #, compared to HCG group; &, compared to nPAH-CHD group; ▲, compared to PAH-CHD group.

Hemodynamic data are shown in Table 2. The measurements of right atrial mean pressure(mRAP), right ventricular mean pressure(mRVP), mean pulmonary artery pressure(mPAP), systemic vascular resistance(SVR), pulmonary vascular resistance (PVR) and SVR/PVR in PAH-CHD and IPAH patients were significantly higher than that in nPAH CHD patients(P<0.05). The measurements of pulmonary artery flow(Qp), systemic artery flow(Qs), oxygen saturation of mixed venose blood(SvO2), Cardiac index(CI) in PAH-CHD and IPAH patients were significantly lower than that in nPAH-CHD patients(P<0.05, Table 2). The measurements of mRVP, mPAP, PVR, SVR/PVR in PAH-CHD patients were significantly higher than that in nPAH-CHD patients(P < 0.05, Table 2).

### 3.3 P wave duration

The maximum P wave duration(Pmax), PWD were higher in PAH, PAH-CHD, IPAH patients than in HCG and nPAH-CHD patients(P 0.05). The minimum P wave duration (Pmin) was higher in PAH-CHD patients than in HCG(P 0.05). The Pmin was lower in IPAH patients than in nPAH-CHD and PAH-CHD group(P 0.05). (Table 3).
Table 3 Comparison of P wave duration data between groups

<table>
<thead>
<tr>
<th></th>
<th>PAH group (n=103)</th>
<th>PAH-CHD group (n=59)</th>
<th>IPAH group (n=44)</th>
<th>nPAH-CHD group (n=30)</th>
<th>HCG group (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmax ms</td>
<td>111.49±14.53*</td>
<td>113.69±14.85*</td>
<td>108.53±13.71*</td>
<td>100.76±10.16*</td>
<td>90.89±8.80</td>
</tr>
<tr>
<td>Pmin ms</td>
<td>60.24±13.35</td>
<td>63.44±12.31*</td>
<td>55.96±12.43 ▲</td>
<td>62.88±8.38</td>
<td>57.83±12.19</td>
</tr>
<tr>
<td>PWD ms</td>
<td>51.24±10.47*</td>
<td>50.25±12.15*</td>
<td>52.57±7.62#</td>
<td>37.49±9.82</td>
<td>33.06±10.04</td>
</tr>
</tbody>
</table>

Values are mean±SD or numbers (percentages). * means the variable does not conform to a normal distribution. A p value 0.05 was considered statistically significant. Pmax: The maximum P wave duration; Pmin: The minimum P wave duration; PWD: P-wave dispersion; #, compared to HCG group; &, compared to nPAH-CHD group; ▲, compared to PAH-CHD group.

There was a strong negative correlation between PWD and TAPSE (r = -0.717, p< 0.001) (Figure 1). There was a positive correlation between PWD and RVD (r=0.342, p<0.01), RAS (r=0.375, p<0.01), and mPAP (r=0.577, p<0.01), PVR (r=0.554, p<0.01) calculated from RHC (Figure 1).

3.4 Comparison of PWD indexes between groups of PAH patients with different risk stratification

We quantified 103 PAH patients by risk stratification into three groups: 30 in the low-risk group, 53 in the medium-risk group, and 20 in the high-risk group. The study found that there were significant differences in PWD among low-risk, middle-risk and high-risk groups (43.89±9.91, 51.29±6.61, 62.15±10.44, all P<0.05) (Figure 2). Correlation analysis found that PWD was positively correlated with the quantitative value of risk stratification in PAH patients (r=0.592, P<0.001).

3.5 ROC curve analysis of PWD levels

When the Jordan index (sensitivity + specificity −1) reached the maximum value, the corresponding PWD value was the diagnostic threshold. When the cut-off value of PWD was set at 41.45ms, the sensitivity was 95.45%, the specificity was 86.67%, the PPV was 91.30%, the NPV was 92.86%, the accuracy was 91.89% and the AUC was 0.939 in predicting IPAH (P <0.001, Figure 3A). When the cut-off value of PWD was set at 41.5ms, the sensitivity was 84.75%, the specificity was 86.67%, the PPV was 92.59%, the NPV was 74.29%, the accuracy was 85.39% in predicting PAH-CHD, with the area under the curve (AUC) of 0.872 (P <0.001, Figure 3B).

Discussion

The main finding of this study was that PWD levels in PAH-CHD and IPAH patients were significantly increased. When PWD was 41.5ms, it had higher diagnostic value for PAH-CHD, and when PWD was 41.45ms, it had higher diagnostic value for IPAH.

Dilaveris et al[7] first described PWD as the difference between the maximum and minimum P-wave durations measured on a standard 12 lead surface electrocardiogram, and showed that it was a sign of sinus pulse non-uniformity and discontinuous transmission. They also observed that the increase of PWD increased the risk of AF[7]. In addition, the correlation between atrial and intra-atrial conduction abnormalities and atrial fibrillation induction has been fully demonstrated[4]. Studies have confirmed that patients with PAH complicated by AF are more likely to get worse, and are a sign of poor prognosis, suggesting that atrial electrical remodeling may occur in patients with PAH[8, 9], so this index can be used clinically to evaluate severity of atrial remodeling.

We found that the levels of Pmax and PWD in the PAH-CHD group were significantly higher than those in the nPAH-CHD group and the HCG, which was consistent with the research results of Fatih Sap et al[10]. These results suggest that the atria of PAH-CHD patients undergo significant electrical remodeling, which further affects the conduction velocity of electrical activity. The reason may be that long-term right ventricular pressure overload in PAH-CHD patients leads to right ventricular dilation, hypertrophy and diastolic dysfunction, which further causes atrial enlargement and fibrosis. Atrial enlargement can lead to severe conduction velocity slowdown[11]. Under the action of PH, the atrium is pulled by continuous mechanical force, resulting in the changes of atrial muscle structure and the dispersion of electrophysiological characteristics, which will aggravate the heterogeneity of atrial myoelectrical activity, and then increase the differences of autonomy and excitability between different parts of the atrium, resulting in significant differences in ECG vector and dispersion of electrical activity in different parts of the atrium. On the surface ECG, there will be increased differences in P wave duration in different leads[10]. We also found that the levels of Pmax and PWD in the IPAH group were significantly increased, and the duration was significantly longer than that in the control group or the nPAH-CHD group. However, different from previous studies[12], the Pmax in nPAH-CHD group was significantly higher than that in control group, which may be due to the presence of shunts during the development of CHD, the volume load and pressure of the right atrium increased, resulting in right atrial enlargement and fibrosis. Finally, the conduction velocity of atrial myoelectric activity is slowed down and the degree of heterogeneity is increased. This may be related to the younger age, shorter disease duration and data bias of the nPAH-CHD group included in previous studies[12].
Our study further revealed RVD, RAS, PA were higher in PAH and nPAH-CHD patients than HCG, and TAPSE was lower than HCG. The RVD, RAS and PA were higher in PAH patients than nPAH-CHD. We further find that there was a strong negative correlation between PWD and TAPSE, and a positive correlation between PWD and RVD, RAS. These findings are consistent with the pathophysiological changes and disease progression of PAH. Asmaa Saleh et al retrospectively analyzed 40 PAH-CHD patients and found that PWD was positively correlated with RVD ($r = 0.498$, $P = 0.02$), consistent with our study[13]. In addition, another study found that when the TAPSE value of PAH patients was lower than 18 mm, it indicated that the right ventricular systolic function and remodeling were impaired, and the prognosis was worse than that of the TAPSE value higher than 18 mm[9].

Right ventricular function is the main factor affecting the prognosis of PAH patients, and hemodynamic parameters reflecting right ventricular function are often used to evaluate the prognosis of PAH patients. Right ventricular function (RVEF) decreased to less than 40% indicates poor prognosis[14]. We found that the hemodynamic parameters such as mRAP, mRVP, mPAP, SVR and PVR in patients with PAH-CHD and IPAH were significantly higher than that in patients with nPAH-CHD. On the other hand the levels of Qp, Qs, Qp/Qs, SvO$_2$, CI were significantly lower in patients with PAH-CHD and IPAH than nPAH-CHD patients. We further find that there was a strong positive correlation between PWD and mPAP, PVR calculated from RHC. The above results indicate that PWD is closely related to hemodynamic parameters reflecting right ventricular function. The National Institutes of Health registry showed that increased mPAP, increased mRAP, and decreased CI were associated with increased mortality[15]. Several studies have shown that mPAP, PVR, and CI are independent risk factors for the prognosis of death in PAH patients, suggesting that PWD may be closely related to the prognosis of PAH[16, 17]. In addition, in our study, the levels of SvO$_2$ and CI in the IPAH group were lower than those in the PAH-CHD group, and the mRAP, SVR and PVR levels in the IPAH group were higher than those in the IPAH group. It suggests that IPAH patients have severe disease and worse prognosis than PAH-CHD patients, which is consistent with present study[18].

The 2015 ESC/ERS guidelines define PAH risk stratification to predict long-term outcomes by assessing pre-treatment baseline status and post-treatment key clinical indicators. The scale is divided into three risk states: high risk state where annual mortality is expected to be > 10%, medium risk state where annual mortality is expected to be 5%-10%, and low risk state where annual mortality is expected to be < 5%[2]. In 2017, the European Journal of Cardiology conducted a quantitative stratification of risk assessment indicators based on this. According to the risk stratification method, we divided all PAH patients into three groups: low-risk, medium-risk and high-risk. The results showed that there were significant differences in PWD levels among the groups, and with the increase of risk stratification, it has an increasing trend. Retrospective analysis of three major registered research centers in Europe and the United States (a total of 3135 patients) showed that there were significant differences in 5-year survival or transplant free survival between baseline and first follow-up[6, 19, 20]. It is suggested that PAH risk stratification is of great significance to guide the formulation of clinical diagnosis and treatment plan and judge the prognosis of patients. Our study has confirmed that PWD level is positively correlated with risk stratification, further indicating that PWD is a good index to evaluate the condition and prognosis of PAH patients. At the same time, through ROC curve analysis, we found that PWD has high sensitivity in predicting PAH-CHD and IPAH, suggesting that PWD can better assist in the diagnosis of PAH.

There were some limitations to our study. First, this is a single center study. In addition, this study only included patients with PAH-CHD and IPAH. The diagnostic and prognostic value of PWD in different types of PAH remains to be further studied. Finally, risk stratification was selected to indirectly evaluate the relationship between PWD and prognosis. There was no long-term follow-up and cardiovascular events as the end point. Whether PWD is an independent risk factor for the prognosis of PAH patients needs further study.

Conclusions
PWD level in PAH-CHD and IPAH patients increased significantly. PWD may be a useful electrocardiogram indicator for early diagnosis, disease assessment and prognosis of PAH patients.

Declarations
Acknowledgements
None.

Authors’ contributions
Jun Luo and Jingjie Sun planned the project, recruited subjects and wrote the manuscript.
Li Xu, Jingyuan Chen, Yusi Chen, Wenjie Chen, Haihua Qiu enrolled subjects and performed the research;
Xiaolin Luo and Sisi Chen analyzed and interpreted the data;
Jiang Li obtained funding for the study, designed and supervised the study.
This study was primarily done in the Second Xiangya Hospital of Central South University. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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**Availability of data and materials**

The datasets generated and analysed during the current study are not publicly available due regulations of the Ethics Committee but are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

All patients signed informed consent to the study. The study protocol was approved by the Ethical Committee of The Second Xiangya Hospital of Central South University. The study was performed in accordance with the Declaration of Helsinki.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no conflicts of interest to disclose.

**References**


Figures
Correlations between PWD and TAPSE, RVD, RAS, mPAP, PVR. Scatter plots of the relationship between P-wave dispersion (PWD) and tricuspid ring systolic displacement (TAPSE)(A); right ventricular diastolic diameter (RVD)(B); right atrial systolic diameter (RAS)(C); mean pulmonary artery pressure (mPAP)(D), and pulmonary vascular resistance (PVR)(E).

**Figure 2**

Comparison of PWD among low-risk group, medium-risk group and high-risk group. #: compared to low-risk group; &: compared to medium-risk group.

**Figure 3**

ROC curve analysis of PWD level. ROC, receiver operating characteristic curve. (A) idiopathic pulmonary hypertension (IPAH); (B) pulmonary arterial hypertension secondary to congenital heart disease (PAH-CHD).