Relationship between P-wave dispersion, left ventricular mass index and function in Nigerian hypertensive patients

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Abstract

Hypertension is the most prevalent cardiovascular disorder in the world. It is associated with target-organ damage in various organs and ECG changes. P-wave dispersion (PWD), which represents inhomogeneous atrial conduction and discontinuation of impulses, has been observed, when prolonged, to predict atrial fibrillation, particularly in the setting of hypertension. This study of PWD in 150 hypertensive patients and controls sought to determine the prevalence of PWD in Nigerian hypertensives and its relationship to left ventricular mass index and left ventricular function.

Mean PWD in normal subjects was $32.14 \pm 4.72$ ms and was significantly shorter than that in hypertensive patients at $38.29 \pm 8.02$ ms. In the total population, 51.3% had prolonged PWD ($>33.46$ ms); 70% in the hypertensives and 32.7% of controls. The only significant difference in hypertensives with prolonged and normal PWD was the waist circumference. There was a negative correlation between PWD and ejection fraction ($r = -0.17$, $p = 0.03$), but not with diastolic function.

Keywords: P-wave dispersion, hypertension, Nigeria

Non-communicable diseases, including cardiovascular diseases (CVD) such as congestive cardiac failure, coronary heart disease, transient ischaemic attack (TIA), stroke, diabetes, cancers and chronic respiratory diseases, constitute a global problem. Hypertension [defined as systolic (SBP)/diastolic blood pressure (DBP) $\geq 140/90$ mmHg] in adults aged 18 years and over was around 22% in 2014, and was recently estimated at 30 to 35%.

Hypertension is the single most important cardiovascular risk factor affecting adults of low- to middle-income countries. Studies in Nigeria have reported a prevalence of hypertension from eight to 46.4%, with a higher prevalence in urban than rural areas. The pooled prevalence increased from 8.6% in 1970–1979 to 22.5% in 2000–2011, and in 2015 to 28.9%.

In a review of target-organ damage and cardiovascular complications in hypertensives aged 18 to 64 years, prevalence of left ventricular hypertrophy (LVH) was 27.9% of the subjects, atrial fibrillation 16.4%, micro-albuminuria 12.3% and overt proteinuria 15.3%. Stroke was present in 6.3%, heart failure in 4.6%, retinopathy in 2.2%, ischaemic heart disease in 1.7% and peripheral vascular disease in 3.6%.

P-wave dispersion (PWD) is defined as the difference between maximum and minimum P-wave duration on the surface ECG. It is believed to represent an inhomogeneous atrial conduction and discontinuous propagation of impulses. It also measures heterogeneity of atrial depolarisation on a 12-lead ECG.

PWD has been found to be a useful predictor of paroxysmal atrial fibrillation, as well as predicting the transition from paroxysmal to persistent atrial fibrillation. PWD and left ventricular mass index (LVMI) have been shown to increase in children with hypertension. PWD tends to be longer in boys than girls and is generally longer in trained athletes than in sedentary individuals.

Some antihypertensives have been shown to reduce PWD and P-wave duration. Such drugs include quinapril, irbesartan, nebivolol and atenolol. These drug effects may, in addition to controlling blood pressure, help in reducing the risk of atrial fibrillation in hypertensives. It has also been observed that PWD is increased in patients with left ventricular diastolic dysfunction and has a weak correlation with left ventricular ejection fraction (LVEF).

We therefore set out to determine the pattern and relationship between PWD, LVMI, left ventricular systolic and diastolic function and blood pressure in a population of hypertensives.
attending the medical out-patient clinics of the Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, Nigeria.

Methods

This was a cross-sectional, comparative study involving consecutive consenting hypertensive subjects and normotensive controls. Patients were recruited from those attending the cardiology out-patient clinic and the general out-patient department of OOUTH.

Inclusion criteria were adults aged 18 years and older, self-reported history of hypertension or use of antihypertensives, blood pressure ≥ 140/90 mmHg or on antihypertensive medication. Hypertensive patients on drugs known to alter P-wave duration (e.g. irbesartan, quinapril, valsartan, ramipril) were excluded from the study.

Age- and gender-matched non-hypertensive controls were recruited from the general population, staff and relatives of patients who gave consent. They were healthy with no obvious organ disease, such as liver pathology, thyroid dysfunction, adrenal disorders, or chronic kidney disease.

All subjects gave informed consent. Approval for the study was obtained from the institution Health Research and Ethics Committee.

Eligible participants had a complete history taken and physical examination done. Information collected from each participant included socio-demographic data, past medical history of congenital heart disease, diabetes, any evidence of endocrine dysfunction, chronic kidney disease, any past hospitalisation and surgical history, family history of hypertension and detailed drug history.

Examination included weight and height to calculate body mass index (BMI). Hip and waist circumference (WC) were recorded to determine the waist/hip ratio. Blood pressure (BP) was measured using appropriate cuff sizes connected to an Accoson branded mercury sphygmomanometer. Readings were taken with the arm positioned at the level of the heart, after participants had been seated and rested for at least five minutes.

A standard 12-lead ECG was done for all participants using the Schiller AT-1 ECG machine in the cardiac laboratory; a hard copy was printed, scanned and saved for measurements. The Mindray BeneHeart R3 ECG machine was also used; with its added advantage of auto-saving all ECG tracings, this was stored for onward enlargement and digital measurement for better accuracy.

Measurement of P-wave maximum and PWD; on the ECG, the P wave was identified in all leads as the first positive, negative or isoelectric deflection before the QRS complex, and its duration was measured manually with ECG callipers. Its duration was measured at the onset; at the beginning of its deflection (positive or negative) in the isoelectric line-up to its termination in the same line. The P-wave duration was measured on all leads in at least three consecutive cycles, and the mean recorded P-wave maximum was taken as the longest measured P wave. The minimum P-wave value was taken as the lowest measured value and PWD was calculated as the difference between the maximum and minimum P-wave duration.

To qualify for analysis, there had to be visible P-wave amplitude in at least eight out of the 12 standard ECG leads, including leads II and V1, and absence of any arrhythmias on the ECG. All readings in the 12 leads were considered. However measurements in leads where the P-wave amplitude was either too small or indistinct were discarded. Measurements were taken over three consecutive cycles.

In this study, participants with PWD > 33.46 ms were deemed to have prolonged PWD; this was based on a meta-analysis of PWD studies done among healthy individuals. Echocardiography was performed using the Philips ClearVue echo-machine and a 3.5-MHz linear array transducer in the cardiac laboratory. Measurements were obtained according to the American Society of Echocardiography (ASE) leading-edge to leading-edge criteria. Left ventricular systolic function (LVSF) and diastolic function (LVDF) were assessed according to the guidelines of the ASE recommendations. In this study, indices for assessing abnormal LVSF was taken as EF < 50% for both male and female.

We used semitransmitral Doppler velocities and tissue Doppler, as recommended by the ASE, of the septal, lateral mitral annulus. However for those with normal or preserved EFs, more parameters than mitral inflow were needed. Pulsed-wave tissue Doppler imaging was performed in the apical four-chamber view to acquire septal and lateral mitral annular velocities. Septal e' and lateral e' were acquired and E/e' was calculated. All these parameters were combined together to further help make a conclusion on diastolic dysfunction. Septal e' < 7 cm/s and E/e' > 15 were considered to be diastolic dysfunction.

Statistical analysis

Data obtained were coded and entered into a computer for analysis. Statistical analysis was done using the Statistical Package for Social Sciences Software (SPSS) version 21. Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as percentages, frequency tables and charts, as appropriate.

Differences in categorical variables were assessed with chi-squared analysis while the student's t-test was used for continuous variables that were normally distributed. The unpaired t-test was used for comparison of continuous variables between groups. Pearson’s linear correlation was used for normally distributed numerical data. This was used to assess the relationship of PWD and LVMI, EF, LVSF, LVDF (using E/ septal e’), systolic and diastolic blood pressures. A value of p < 0.05 was considered statistically significant.

Results

This study comprised 150 subjects and 150 controls. Of the subjects, 72 (48.0%) were males while among the controls, 76 (50.6%) were males. The mean age of subjects was 49.38 ± 11.31 years while that of the controls was 47.14 ± 11.72 years (p = 0.09). The median of hypertension duration among subjects was 48 months, the range being one to 360 months (Table 1).

The mean BMI of subjects (26.84 ± 3.64 kg/m²) was significantly higher than that of the controls (25.32 ± 3.22) (p ≤ 0.001). And the mean WC of the subjects was also more (95.74 ± 11.08 cm) vs 92.24 ± 9.62 cm) (p = 0.004).

The mean P-wave maximum duration (P_max) of the subjects was significantly longer than that of the controls (114.62 ± 16.28 ms; p ≤ 0.001). The mean P-wave minimum was 59.62 ± 11.08 ms in the subjects compared to 59.34 ± 11.52 ms in the controls (p = 0.89).

The mean maximum P-wave duration (P_max) of the subjects was 33.46 ms, which was significantly longer than that of the controls (30.72 ms) (p = 0.032). This P_max value was used as the cut-off for prolonged PWD. The incidence of prolonged PWD was higher (25%) in the hypertensive group compared to the control group (7%). The mean PWD in the hypertensive group was 33.46 ms, while it was 30.72 ms in the control group (p = 0.032). This difference was statistically significant.
duration (P_{min}) of the subjects was 82.31 ± 32.11 ms. The mean PWD of the subjects was also longer (38.29 ± 14.90 ms; p < 0.001).

The mean SBP of the subjects increased significantly with prolonged PWD while 49 (32.7%) had normal PWD (32.11 ± 4.72 ms, p = 0.001).

In this study all participants with PWD > 33.46 ms were deemed to have prolonged PWD; the prevalence of prolonged PWD among subjects was more than that of the controls (70.0% vs 32.6%; p < 0.001). Furthermore, in the 105 subjects with prolonged PWD, their mean PWD was 42.06 ± 6.31 ms compared with the 49 controls with prolonged PWD whose mean PWD was 37.68 ± 3.07 ms. This difference was statistically significant (Table 1).

Table 2 shows the comparison of clinical, ECG and echo parameters among subjects with prolonged and normal PWD. One hundred and five (70%) of the subjects had prolonged PWD while 49 (32.7%) had normal PWD (p < 0.0001). Mean PWD was significantly longer in subjects with prolonged PWD, compared to those with normal PWD (42.06 ± 6.31 vs 29.52 ± 3.34; p < 0.0001). There was no significant difference in the age distribution of subjects with normal and prolonged PWD.

Comparing their clinical parameters, such as mean SBP, DBP, BMI, WC and duration of hypertension in months, only the mean WC of the subjects increased significantly with prolonged PWD. Among subjects with prolonged PWD, 25 (24.7%) had LVH (ECG) compared to 15 (34.1%) subjects with normal PWD. This difference was not significant (p = 0.21). Again, the mean left atrial diameter (LAD) and LVMI were slightly higher in subjects with prolonged PWD compared to those with normal PWD, but not statistically significant.

Table 3 shows the correlation of PWD with LVMI, and left ventricular systolic and diastolic function among the hypertensive subjects. There was no correlation between the mean PWD and mean LVMI among hypertensives (r = 0.08, p = 0.33), although a negative correlation existed between mean PWD and EF (r = −0.17, p = 0.03) and a significant almost linear relationship between PWD and WC (r = 0.23, p = 0.004). Other associations are shown in Table 3. A Pearson's correlation was also done between ECG LVH and LVMI in the subjects and a weak but significant association was found (r = 0.20, p = 0.02).
compared to their controls (30.3 ± 6.6 ms), with a similar mean age distribution of 49 ± 10.6 years. This corroborates what is documented in the literature.\textsuperscript{9,11,12,20}

This study also showed that $P_{\text{max}}$ duration was significantly longer in the subjects than in the controls, which is in agreement with findings by Dagil \textit{et al.}.\textsuperscript{18} However the mean $P_{\text{max}}$ duration in this present study was longer than that reported by Dagil \textit{et al.} This difference is largely methodological; Dagil \textit{et al.} used a cut-off point of $\geq 110$ ms while $\geq 120$ ms was used here. Arijara et al.\textsuperscript{19} recommended $> 120$ ms as the cut-off point, which increases the specificity of identifying prolonged PWD and reproducibility.

The prevalence of $P_{\text{max}} > 120$ ms in this study was 31\% lower than in that by Asad \textit{et al.} who found a prevalence of 47\% in a hospitalised population. Methodological differences may account for this. Their patients were an elderly in-patient population with co-morbidities, which alone might have caused increased $P_{\text{max}}$ duration and introduced confounders. Our study comprised middle-aged out-patients.

In this study, the prevalence of prolonged PWD was 70\% higher in the subjects than the 30\% found in the controls. This is likely due to the effect of hypertension on the atrial myocardium causing non-uniform contraction, prolonged electrical activation time, left atrial stiffness, increasing left atrial pressure and remodelling.\textsuperscript{28,29} Prolonged PWD has also been associated with the development of paroxysmal atrial fibrillation because it reflects an abnormal electrophysiology due to atrial remodelling, stiffness and inhomogeneity in atrial conduction. \textsuperscript{29,30}

BMI and WC significantly correlated with prolonged PWD and $P_{\text{max}}$ in the subjects compared to the controls, which is comparable with the study by Dagil \textit{et al.}\textsuperscript{18} and Nussinovitch \textit{et al.}\textsuperscript{9} They observed that there was a significant difference in obese subjects with a BMI $\geq 30$ kg/m$^2$. Other studies have shown a significant reduction in PWD with a reduction in BMI after a 12-week weight-loss programme, with a positive correlation between the decrease in level of PWD and percentage weight loss.\textsuperscript{31} These observations may suggest that substantial weight loss is associated with improvement in atrial repolarisation, as reflected by improved P-wave indices.

In this study, prolonged PWD correlated significantly with increased WC, which is an important independent cardiovascular risk factor. According to Dobbelsteyn \textit{et al.},\textsuperscript{17} central fat distribution has always been associated with worse cardiovascular risk and WC may be the best single indicator of other multiple cardiovascular risk factors.

An association of $P_{\text{max}}$ duration and PWD with a sharp increase in blood pressure has been observed.\textsuperscript{14} It has also been shown that in hypertensive urgency, the use of medications and subsequent reduction of $P_{\text{max}}$ and PWD significantly caused a stability in atrial conduction and haemodynamics.\textsuperscript{14} In a subset of pre-hypertensive subjects,\textsuperscript{11} it has been shown that PWD increased significantly with rising blood pressure compared to normal blood pressure ($< 120/80$ mmHg).

Mean LVMI was significantly higher among the subjects compared to the controls, so it was also higher among the study population with prolonged PWD than in those with normal PWD. However, comparing within the subject group, between those with prolonged and those with normal PWD, their PWD was not statistically significant. The reason for this is unclear.

In this study, there was no significant association between subjects with prolonged PWD and LVMI ($r = 0.08, p = 0.33$). This is similar to a Nigerian hypertensive study by Ale \textit{et al.} where a lack of relationship was found between QT dispersion (QTd) and LVMI.\textsuperscript{30} This may be due to the effect of antihypertensive therapy on atrial and ventricular remodelling,\textsuperscript{27} as most of the hypertensive patients in this study were already on medication.

In a paediatric study on the relationship of PWD, LVMI and blood pressure among school children,\textsuperscript{19} it was reported that there was a significant increase in PWD and LVMI among hypertensive children, although some children with a normal LVMI still had increased PWD. This latter finding supports the theory by Martin Gracia \textit{et al.}\textsuperscript{27} that intra-atrial and inter-atrial conduction disorders, expressed by increased PWD in structurally normal hearts, are present before anatomical disturbances appear.

In this study, the mean EF was significantly longer in the controls compared to the subjects. There was a significant negative correlation between PWD and EF. With increasing PWD there is a tendency to decreased LV systolic function. This is in agreement with Huseyin \textit{et al.}\textsuperscript{25} who reported a weak but significant correlation between PWD and EF. Also Ding \textit{et al.}\textsuperscript{32} reported that PWD improved with an improvement in EF after cardiac resynchronisation therapy. These findings further strengthen the hypothesis that PWD may be used as a non-invasive marker for target-organ damage, as it has been shown in this study that a longer PWD correlated with poorer systolic function.

The ability of PWD to reflect diastolic dysfunction may be due to the haemodynamic and structural effects of left ventricular diastolic dysfunction (LVDD) on left atrial structure and function, which is represented by the P wave on ECG.\textsuperscript{25} In this study all parameters were considered to determine prevalence of LVDD. The mean E/e', E velocity, E/A ratio and septal e' were significantly different among the subjects compared to controls and also different in the proportion of the study population with prolonged PWD. However, comparing the subjects with normal and prolonged PWD, the mean E/e' was comparable.

Once there is increased LV filling pressure in the setting of hypertension, there is elevated left atrial pressure, which may be associated with inhomogeneous and non-uniform atrial conduction, manifesting as prolonged P-wave duration on ECG and left atrial enlargement.\textsuperscript{29}

Left atrial enlargement is regarded as a surrogate of LVDD.\textsuperscript{39} In this study, mean left atrial diameter was significantly increased in subjects alongside the prolonged PWD. In this study E/e' did not correlate clinically with prolonged PWD among the subjects, unlike in the study by Tsai \textit{et al.},\textsuperscript{28} who reported a significant clinical correlate between corrected PWD and the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity. Also the prevalence of LVDD was higher in the group with corrected PWD.

Although in this study the mean E/e' was significantly increased among subjects compared to the controls, there was no statistical difference between the mean E/e' of subjects with prolonged and normal PWD. However, Wei-chung \textit{et al.}\textsuperscript{34} found an association of increased arterial stiffness and PWD with LVDD; increased PWD correlated with higher E/e' indices, suggesting LVDD. These findings may help us conclude that PWD is a useful screening tool to identify LVDD in high-risk groups such as hypertensives.
Conclusion
The mean PWD in normal Nigerian subjects was 32.1 ± 14.72 ms and it was significantly lower than in hypertensive patients, at 38.29 ± 8.02 ms. The prevalence of prolonged PWD was 51.3% in the total study population, 70% among subjects and 32.7% among controls. Whereas there was a relationship between PWD and LVDF, there was no relationship between LVMI and PWD. There was an inverse relationship with PWD and EF, but no association was found between PWD and LVDF using E/e'.

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References
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