ORIGINAL ARTICLE

P-wave dispersion and left atrial indices as predictors of paroxysmal atrial fibrillation in patients with non hemorrhagic cerebrovascular strokes and transient ischemic attacks

Mohamed Elansary, Mohamed Hamdi, Hanan Zaghlal, Dalia Ragab *

Critical Care Medicine Department, Cairo University, Egypt

Received 13 September 2013; accepted 20 October 2013
Available online 14 February 2014

KEYWORDS
P-wave dispersion;
LA volume;
Paroxysmal AF

Abstract  Background: One-third of stroke and Transient Ischemic Attack (TIA) are cryptogenic requiring additional investigation and intervention. Occult Paroxysmal Atrial Fibrillation (PAF) has been suggested as a possible cause for these cryptogenic strokes.

Objective: The aim of our study is to evaluate the role of simple ECG & bedside echocardiographic parameters for prediction of PAF in patients presenting with stroke or TIAS.

Patients & methods: The study included 60 patients with non hemorrhagic stroke. During 1 week of continuous ICU monitoring, 30% of patients had PAF (group 1), the remaining 42 patients did not develop PAF (group 2). All patients were subjected to detailed history taking, thorough clinical examination including NIHSS, serial ECGs for calculation of maximum and minimum P wave duration (Pmax & Pmin), and P wave dispersion (Pdis), and transthoracic echocardiography for calculation of left atrial volume (LAV), and left atrial volume index (LAVI).

Results: It was found that Pmax & Pdis were significantly higher in group 1 in comparison to group 2 (147.7 ± 9.6 mm vs 114.3 ± 9 mm, P<0.001) and (54.1 ± 7.5 mm vs 30.2 ± 7 mm, P<0.001), respectively. Also LAV & LAVI were significantly higher in group 1 compared to group 2 (57.1 ± 10 mm vs 40.1 ± 12 mm, P<0.001) & (28.9 ± 3 mm²/m² vs 20.1 ± 8 mm²/m², P<0.001), respectively. On multivariate logistic regression analysis Pmax, Pdis, and LAVI were the most significant independent predictors of PAF.

Conclusion: PAF is a possible etiology of patients with ischemic cerebrovascular accidents patients even in those who had normal sinus rhythm on admission. Pmax ≥ 125 mm, Pdis ≥ 40 mm, and LAVI ≥ 24 are highly significant predictors of PAF with PPV of 99%, 96% and 78%, respectively.

* Corresponding author. Tel.: +20 1225424473.
E-mail address: dmragab@yahoo.com (D. Ragab).

Peer review under responsibility of Egyptian Society of Cardiology.

1110-2608 © 2013 Production and hosting by Elsevier B.V. on behalf of Egyptian Society of Cardiology.
http://dx.doi.org/10.1016/j.ehj.2013.10.004
1. Introduction

Stroke is the second leading cause of death worldwide and the third leading cause of death in the developed world. Atrial fibrillation (AF) is the commonest cardiac arrhythmia and constitutes the etiology in almost 15–20% of all ischemic strokes. A paroxysmal variant is as dangerous as permanent one, and in case of stroke, it is probably as frequent as in permanent variant in causing the most severe and disabling stroke and might be overlooked and this might lead to depriving patients from full anticoagulation therapy. Therefore, it is important to diagnose AF whether permanent or paroxysmal variants after an ischemic stroke to provide maximal stroke prevention therapy. However, the diagnosis of AF especially the paroxysmal variant poses a challenge. Some reports revealed that the measurement of P wave duration and P wave dispersion in sinus rhythm, together with left atrial echocardiographic parameters might be a useful noninvasive clinical tool to identify patients at risk of developing atrial electrical instability and AF.

2. Aim of the study

To determine whether ECG and transthoracic echocardiographic LA measurements could help in detecting PAF in patients presenting with acute ischemic cerebrovascular accidents.

3. Patients and methods

This study is a prospective observational study conducted on 60 patients with mean age of 64.3 ± 10.9 years admitted to the Critical Care Medicine Department of Cairo university with the diagnosis of acute ischemic cerebrovascular stroke or TIA during the period from July to December 2012. All patients had normal sinus rhythm at the time of admission.

Exclusion criteria included: patients less than 18 years old, rheumatic heart disease or ICU length of stay less than one week. All patients were subjected to detailed history taking, thorough clinical examination including full neurological assessment, routine laboratory investigation. CT brain was done on admission and 48 h later for all patients. Upon admission, assessment of conscious level using Glasgow Coma Scale (GCS), National Institute of Health & Stroke Score (NIHSS) & Modified Rankin Score (MRS). Twelve lead ECG was done on admission and regularly every 8 h for 7 days. All ECGs were recorded at a paper speed of 25 mm/s & 50 mm/s with a calibration of 1 mV = 10 mm and analyzed thoroughly for calculation of $p_{\text{max}}, p_{\text{min}}, \text{and } p_{\text{dis}}$. P-wave duration was defined as the time measured from the onset to the end of the P-wave deflection. The onset of the P-wave was considered as the junction between isoelectric line and first visible upward or downward slope of the trace, the return of the trace to its isoelectric line was considered to be the end of the P-wave. $p_{\text{dis}}$ was defined as the difference between maximum and minimum P-wave durations.

Transthoracic echocardiography was done for all patients: Standard 2D, M mode, pulsed and color Doppler using parasternal and apical views to measure dimensions and evaluate global and regional left ventricular function. Assessment of left atrial volume (LAV) using the prolate ellipse method at apical 4-chamber and parasternal long-axis views at ventricular end systole (Fig. 1).

LAV was calculated as $D_1 \times D_2 \times D_3 \times 0.523$. Left atrial volume index (LAVI) was calculated by relating the LAV to body surface area. During ICU stay, all patients were kept on continuous rhythm monitoring using monitors with trends for detection of any rhythm disturbance.

Patients were divided into 2 groups: group 1: 18 patients who had PAF identified by documented history or during ICU stay. Group 2: 42 patients who had normal sinus rhythm during their whole hospital stay.

3.1. Statistical analysis

Computer software package SPSS 15.0 was used in the analysis. For quantitative variables, mean/median (as a measure of central tendency), standard deviation/range, minimum, and maximum (as measures of variability) were presented. Frequency and percentages were presented for qualitative variables. Mann–Whitney, Kruskal Wallis and Patients & Methods-83-Anova tests were used to estimate differences in quantitative variables. Chi-square and Fisher Exact tests were used to estimate differences in qualitative variables. Logistic regression analysis was performed to find out the most significant independent predictors of certain dependent variable by using backward likelihood ratio technique. ROC curve (receiver operator characteristic curve) was used to find out the best cut off in addition to validity. Correlation to estimate association between quantitative variables was presented in the form of correlation coefficient and its significance. A probability value (P value) less than 0.05 was considered significant. P value less than 0.001 was considered highly significant, P value higher than 0.05 was considered insignificant.

4. Results

During the period from July to December 2012, 60 patients admitted with cryptogenic cerebrovascular accidents or TIAs were enrolled. Patients were then divided according to documented history or development of PAF during their hospital stay into 2 groups. Group 1 (PAF group) included 18 patients and group 2 (non PAF group) included 42 patients. Patients’ demographic and general characteristics are shown in Table 1.

Except for diabetes mellitus which was found to be significantly higher in group 2, patients in both groups were comparable to each others with no statistical significant difference as regards their general characteristics namely general epidemiological data, atherosclerotic risk factors, history of thyroid disease, history of previous cerebrovascular accidents or global LV function.
4.1. Comparison between the studied groups regarding severity of stroke

Patients in group 1 had significantly more severe symptoms at presentation compared to patients in group 2, they have lower GCS (11.7 ± 3 vs 13.4 ± 2.9, \(P < 0.05\)), higher NIHSS (13.8 ± 7 vs 9.5 ± 5, \(P < 0.05\)) and higher MRS (3.7 ± 1.1 vs 3.2 ± 1.2, \(P < 0.05\)), Table 2.

4.2. P wave and echocardiographic left atrial indices in study groups

Group 1 had a highly significantly higher values of \(P_{\text{max}}\) (147.7 ± 9.6 vs 114.3 ± 9, \(P < 0.001\)), \(P_{\text{min}}\) (93.6 ± 8 vs 83.7 ± 8, \(P < 0.001\)), \(P_d\) (54.1 ± 7.5 vs 30.2 ± 7, \(P < 0.001\)), LAV (57.1 ± 10 vs 40.1 ± 12, \(P < 0.001\)) and LAVI (28.9 ± 3 vs 20.1 ± 8, \(P < 0.001\)), Table 3.

Receptive operator characteristics (ROC) curve was calculated to detect the highest predictive parameter of Paroxysmal AF (PAF) and it was found that \(P_{\text{max}}\), \(P_d\), and LAVI were considered the most valid predictors of PAF. The best cutoff value of \(P_{\text{max}}\), \(P_d\), and LAVI were 125 ms, 40 ms, and 24 ml/m². These values have 98%, 94%, and 89% sensitivity, 96%, 93%, and 75% specificity, with 99%, 96%, and 90% positive predictive value, 93%, 95%, and 80% negative predictive value, and diagnostic accuracy 94%, 92.7%, 78% and area under the curve (AUC) for these variables were 0.99 0.98, and 0.87, respectively, Fig. 2.

Moreover, \(P_{\text{max}}\), \(P_d\), and LAVI were considered the most significant independent predictors of PAF by backward likelihood ratio technique of logistic regression, Table 4.

5. Discussion

Despite advances in diagnostic and interventional procedures, cardiac causes constitute the etiology in a high proportion of patients with ischemic stroke. The association between PAF and stroke has been shown to be considerably strong. Ischemic stroke patients – either with paroxysmal or permanent AF – have greater mortality and morbidity rates when compared to those without AF. On the other hand, poor outcome associated with PAF is preventable with anticoagulation in nearly 40% of patients and it is clinically crucial to detect these patients. However, unlike permanent AF, PAF might not be diagnosed readily and can be easily overlooked.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>General characteristics of the studied groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Group 1</td>
</tr>
<tr>
<td>Age</td>
<td>67.8 ± 10</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (55.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (44.4%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>8 (44.4%)</td>
</tr>
<tr>
<td>HTN</td>
<td>16 (88.9%)</td>
</tr>
<tr>
<td>DM</td>
<td>7 (38.9%)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>3 (16.2%)</td>
</tr>
<tr>
<td>IHD</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>HF</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Previous Stroke</td>
<td>5 (27.8%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>EF</td>
<td>54.8 ± 14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison between group 1 and 2 as regards admission severity scores.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Group 1</td>
</tr>
<tr>
<td>MRS</td>
<td>3.7 ± 1.1</td>
</tr>
<tr>
<td>GCS</td>
<td>11.7 ± 3</td>
</tr>
<tr>
<td>NIHSS</td>
<td>13.8 ± 7</td>
</tr>
</tbody>
</table>

MRS: Modified Rankin Score, GCS: Glasgow Coma Scale, NIHSS: National Institute of Health & Stroke Score.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>P wave and echocardiographic left atrial indices in both groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Group 1</td>
</tr>
<tr>
<td>(P_{\text{max}})</td>
<td>147.7 ± 9.6</td>
</tr>
<tr>
<td>(P_{\text{min}})</td>
<td>93.6 ± 8</td>
</tr>
<tr>
<td>(P_d)</td>
<td>54.1 ± 7.5</td>
</tr>
<tr>
<td>LAD</td>
<td>4.0 ± 2.0</td>
</tr>
<tr>
<td>LAV</td>
<td>57.1 ± 10</td>
</tr>
<tr>
<td>LAVI</td>
<td>28.9 ± 3</td>
</tr>
</tbody>
</table>

Figure 1 Left axis parasternal, and apical 4 chambers views to measure D₁, D₂, and D₃. D₁ is obtained from apical 4 chamber view, from blood tissue interface at posterior atrial wall to level of mitral annular. D₂ is obtained from the blood tissue interface of the atrial wall to the interatrial septum. D₃ is obtained from the blood-tissue interface of the anterior and posterior walls.
Clinical guidelines recommend that patients with acute ischemic stroke should be evaluated with 24-h inpatient monitoring to detect PAF. But, 24-h Holter monitoring might have a low yield diagnosing only 2.4–9.4% of these patients. Possibility of detecting PAF with 24-h Holter monitoring might be even lower (1–5%). Moreover, it has recently been reported that there was no significant difference between Holter monitoring and serial ECG assessment in AF detection in patients with stroke/transient ischemic attacks. The challenges mentioned above have led to investigations in this area. Pd is one of the most investigated parameters. Pd assessed on a single resting ECG is regarded as a noninvasive electrocardiographic marker which reflects the prolongation of intraatrial and interatrial conduction time in addition to discontinuous propagation of sinus impulses. It has been demonstrated that prolongation of Pd is a risk factor for the development of PAF independent from the presence of structural heart diseases. It also has been shown that Pd might predict transition from PAF to permanent AF.

In previous studies, echocardiographic left atrial diameter (LAD) and premature atrial contractions on Holter monitoring were the predictors of PAF in patients with acute ischemic stroke. But because of high costs and technical inconvenience, standard 12-lead ECG is still the most commonly used technique. P-wave dispersion (Pd) measured from a single ECG is regarded as an electrocardiographic marker of inhomogeneous and discontinuous propagation of sinus impulses.

Our study aimed at evaluate if P-wave measurements on surface 12 lead ECG, and LA measurements on transthoracic echocardiography can predict PAF in patients with non-hemorrhagic cerebrovascular accidents and TIA’s.

To achieve this aim, we studied 60 patients admitted to the Critical Care Medicine Department of Cairo University with the diagnosis of non hemorrhagic stroke or TIA’s and all had sinus rhythm upon admission. We found that 18 patients (30%) experienced paroxysmal attack of AF while 42 patients (70%) remained with normal sinus rhythm during their hospital stay. Both groups showed no statistical significant difference regarding their general characteristics and demographic data. Nonetheless, there was no statistical significant difference between the 2 groups regarding the presence of clinical risk factors except for diabetes that was significantly higher in group 1.

This finding was in agreement with the study conducted by Archit Bhatt et al., who studied the predictors of occult PAF in cryptogenic strokes, they studied and retrospectively analyzed 62 consecutive patients with cryptogenic stroke or TIA who underwent prolonged non-invasive cardiac monitoring up to 28 days after discharge & found that there was no statistical significant difference between AF & non AF group regarding age, sex, hypertension, and heart disease.

In contrast, Wohlforth et al. reported that advanced age & history of IHD could be clinical predictors to identify PAF after ischemic stroke. This discrepancy may be related to the difference in methodology implemented in their study, as their patients were subjected to the intensified algorithm to detect paroxysmal atrial fibrillation (7 days Holter ECG, and follow up investigations after 90 days & one year).

Regarding the severity of stroke at presentation, our study revealed that PAF group had higher NIHSS & lower GCS compared to non AF group (13.8 ± 7 & 11.7 ± 3 vs 9.5 ± 5 & 13.4 ± 2.9, P value <0.05).

In agreement to this finding, Kimura et al. found that the admission National Institutes of Health Stroke Scale (NIHSS) score of the AF group was higher than that of the non-AF group (median, 12 vs 5; P < 0.0001), and that The mortality rate within 28 days after admission was 11.3% in the AF group and 3.4% in the non-AF group (P < 0.0001).

Our results also showed that apart from echocardiographic LA diameter, all other ECG & echocardiographic LA measurements, Pmax, Pdis LAVI, were significantly higher in PAF group compared to non paroxysmal AF group (147.7 mm, 54.1 mm, 57.1 mm², and 28.9 mm²/m² vs 114.3 mm, 30.2 mm, 40.1 mm², and 20.1 mm²/m² respectively, P value <0.05). Results published by Umuttan Dogan et al. reported the same results. In 2012, they conducted a study on 400 patients presenting with acute ischemic stroke, where resting ECG, 24 h Holter monitoring & echocardiography were done to all patients, results showed that Pmax (P = 0.002), Pdis (P < 0.0001) and LA diameter (P = 0.04) were significantly higher in patients with PAF when compared to patients without PAF. However, in binary logistic regression analysis Pdis was the only independent predictor of PAF.

Moreover, Mehrdad Saravi et al. studied the different LA indices in where 40 consecutive patients with PAF and other 40 age and gender matched healthy controls. Their results showed that Pdis were significantly longer in PAF patients with either normal or increased LA diameter than in controls.

In addition, Kosropanah Sh et al. reported that ECGs of patients with and without AF in pre and post-CABG showed that P-wave dispersion increased by 10 ms on the 1st postop day in those with AF compared to pre-op values (P = 0.018). Likewise, P-wave dispersion increased by 8 ms on the 3rd post-op day in patients who developed AF (P = 0.035).

In our study, echocardiographic parameters namely LAVI showed statistically significant higher values in group1 in comparison to group 2 (57.1 ± 10 & 28.9 ± 3 vs 40.1 ± 12 & 20.1 ± 8, respectively, P <0.05).

In agreement with our study, Raol stahenberg et al. performed a study on 193 consecutive patients presenting with cerebro ischemia & normal sinus rhythm, patients were subjected to echocardiographic evaluation & 7 days holter monitoring for

![Figure 2](https://example.com/fig2.png) ROC curve of Pmax, Pmin, Pd and LAVI. Moreover, Pmax, Pd and LAVI were considered the most significant independent predictors of PAF by backward likelihood ratio technique of logistic regression Table 4.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Beta-coefficient</th>
<th>P</th>
<th>Odd’s (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmax ≥ 125</td>
<td>0.90</td>
<td>&lt;0.001</td>
<td>2.7 (1–12.5)</td>
</tr>
<tr>
<td>Pd ≥ 40</td>
<td>0.85</td>
<td>&lt;0.001</td>
<td>2.2 (0.6–11.5)</td>
</tr>
<tr>
<td>LAVI ≥ 24</td>
<td>0.57</td>
<td>&lt;0.001</td>
<td>1.8 (0.2–12)</td>
</tr>
</tbody>
</table>
identification of patients with paroxysmal PAF. Results showed that LAV & LAVI were higher in paroxysmal atrial fibrillation group in comparison to non paroxysmal atrial fibrillation group. In our study, \( P_{\text{max}} \) in ECG is a statistically significant predictor of PAF & with cut off value > 125 ms it predicts PAF with very high sensitivity & specificity 98% & 96%, respectively with a positive predictive value of 99% & negative predictive value of 93%. Also \( P_d \) is a statistically significant predictor of PAF & with cut off value > 40 ms it predicts PAF with very high sensitivity & specificity 94% & 93%, respectively with a positive predictive value of 96% & negative predictive value of 95%.

In comparison to Umuttan Dogan et al., study in binary logistic regression analysis \( P_d \) was the only independent predictor of PAF. The cut-off value of \( P_d \) for the detection of PAF was 57.5 ms (ms). Area under the curve was 0.80 \((P < 0.001)\). On a single 12-lead ECG, a value higher than 57.5 ms predicted the presence of PAF with a sensitivity of 80% and a specificity of 73%.

In our study, LAVI in echocardiography is statistically highly significant predictor of PAF & with cut off values higher than 24 ml/m² it predicts PAF with sensitivity 89% & specificity 75% & with positive predictive value of 90% & negative predictive value of 80%.

In comparison to Raol stahrenberg et al., LAD, LAV, LAVI & LAVI/a’ (LAVI divided by tissue Doppler wave) were all highly sensitive predictors with \( P \) value < 0.05 but in binary logistic regression analysis LAVI/a’ had the largest area under the curve & with cut off value < 2.3 had 92% sensitivity, 55.8% specificity, and 98% negative predictive value for PAF.

6. Study limitation

In addition to the small sample size, identification of occurrence of AF depended only on documented history and recording an AF episode during their ICU stay and none of the study patients underwent more intensified investigation as Holter or was subjected to long follow up. Also, the mean age of study patients was a little bit high making the association of PAF and the etiology of their cerebrovascular accidents questionable, in other words, thrombotic etiology could not be excluded.

7. Conclusion

PAF is a possible etiology of patients with ischemic cerebrovascular accidents even those had normal sinus rhythm during admission. LA indices as \( P_{\text{max}}, P_{\text{dis}}, \) and LAVI are highly significant independent predictors of PAF in these patients.

Conflict of interest

No conflict of interest.

References

10. Andrikopoulos GK, Dilaveris PE, Richter DJ. Increased variance of P wave duration on the electrocardiogram distinguishes patients with idiopathic paroxysmal atrial fibrillation. PACE 2000;23:1127–32.
13. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Chamber Quantification Writing Group; American Society of Echo-cardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology.
22. Koide Y, Yotsukura M, Ando H, et al. Usefulness of P-wave dispersion in standard twelve-lead electrocardiography to predict


