P wave duration in paroxysmal and persistent atrial fibrillation

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Abstract

Functional and structural changes in atrial muscle constitute a substrate for atrial fibrillation. The pathological changes in the left atrium decrease conduction velocity and result in prolongation of the P wave duration. The aim of the study was to assess the duration of the P wave in patients with paroxysmal and persistent atrial fibrillation. The study group consisted of 119 patients diagnosed with atrial fibrillation, 57 women and 62 men, aged 65.3+/-9.4 years. There were 65 patients with paroxysmal AF and 54 with persistent AF. In this group the electrical cardioversion was performed. The P wave duration, was measured using electrophysiological system in all leads at paper speed of 200 mm/s. The studied patients did not differ in term of age, gender and comorbidities. The patients with persistent AF had longer P wave duration (159.9+/-22.3 vs 144.6+/-17.2 ms, p<0.001), higher glucose concentration (119.4+/-33.4 vs 108.0+/-24.6 mg/dL, p=0.015). Those results were not influenced by the anti-arrhythmic treatment. The persistent atrial fibrillation shows prolongation of the P wave duration over the paroxysmal form of the arrhythmia, independently to age, gender and anti-arrhythmic medication. The prolongation of the P wave related to persistent arrhythmia should force the physicians to earlier restoration of the sinus rhythm in order to its more successful long term maintenance. Key words: P wave duration, atrial fibrillation, diabetes mellitus, chronic kidney disease

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The study group consisted of 119 patients diagnosed with atrial fibrillation, 57 women and 62 men, aged 65.3+/-9.4 years. There were 65 patients with paroxysmal AF and 54 with persistent AF. In this group the electrical cardioversion was performed. The P wave duration, was measured using electrophysiological system in all leads at paper speed of 200 mm/s and

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The persistent atrial fibrillation shows prolongation of the P wave duration over the paroxysmal form of the arrhythmia, independently to age, gender and anti-arrhythmic medication. The prolongation of the P wave related to persistent arrhythmia should force the physicians to earlier restoration of the sinus rhythm in order to its more successful long term maintenance.

Key words: P wave duration, atrial fibrillation, diabetes mellitus, chronic kidney disease

Introduction:

Atrial fibrillation is an arrhythmic consequence of multiple pathological processes leading to functional and structural changes in the atrial muscle [1, 2]. Among the major pathologies leading to this arrhythmia are hypertension, coronary artery disease and subsequent heart failure play the major role. Less frequently recently are acquired heart defects and hyperthyroidism, which also promotes atrial fibrillation [3, 4]. Despite treating both atria as a substrate of atrial fibrillation, it is clinically assumed that this arrhythmia occurs mainly due to left atrial pathologies - primarily due to the higher workload it needs to cope with as a consequence of the higher left ventricular resistance. These diseases cause changes in the structure of the atrial muscle through death and apoptosis of cardiomyocytes, contributing to stromal fibrosis. This affects generation of arrhythmia foci, local potential fragmentation and possible re-entry loops. However, the main consequence visible in echocardiography is the left atrial enlargement. This is also the result of an increase in left ventricular filling pressure as well as organic and functional mitral valve regurgitation.

Furthermore, atrial fibrillation is caused by other arrhythmias such as multiple atrial extrasystole, atrial focal tachycardia or atrial flutter [5, 6, 7]. Their constant duration or paroxysm lead to electrophysiological changes in the action potential, usually a shortening of the refractory period, the local intensity of which may be different. This is manifested by heterogeneity of the repolarization process. Repolarization disorders lead to functional conduction disturbances, which, superimposed on structural changes and conduction slowing associated with cardiomyocyte depletion, intensify the re-entry phenomenon and promote the maintenance and persistence of arrhythmias. The described pathologies have an impact on the electrocardiographic picture of the atrial muscle depolarization, depicted by the P wave of the electrocardiogram. With the duration and progression of functional and structural changes, the duration of the P wave prolongs, making it a risk factor for atrial fibrillation [8].

An interesting and clinically important issue is the positive relationship between atrial fibrillation paroxysm and the tendency of the arrhythmia to persist, which was reflected in the term “AF begets AF” created by Wijffels et al. [9]. Rapid atrial arrhythmias affect the functional changes in the process of atrial muscular repolarization and, above all, induce heterogeneity of refraction duration by the formation of local blocks and

slow conduction zones [10]. In addition, atrial fibrillation episodes lead to left atrial enlargement, most likely due to an increase in filling pressure but also due to blood retention and functional mitral regurgitation. All the processes described cause that with time the paroxysmal AF becomes persistent, and finally the decision is made to leave the arrhythmia in a permanent form [4, 10, 11].

All the issues mentioned, indicate the necessity of complex systemic treatment and prevention of AF paroxysms. An important aspect is to reduce the duration of individual episodes using pharmacological or electrical conversion to sinus rhythm. Prolonged arrhythmia paroxysms lead to a deepening of functional and anatomical changes; hence it is likely that patients with persistent atrial fibrillation after sinus rhythm restoration have a longer duration of the P wave compared to patients with paroxysmal form of the arrhythmia.

Purpose:

The aim of the study was to assess the duration of the P wave in patients with atrial fibrillation in different clinical presentations of the arrhythmia.

Material and methods:

The study group consisted of 119 patients diagnosed with atrial fibrillation. There were 57 women and 62 men, aged 65.3+/-9.4 years. The essential co-morbidities were reported. There were 65 patients with paroxysmal AF (AF group), in sinus rhythm during examination and 54 patients with persistent AF. In this group the electrical cardioversion was performed to restore the sinus rhythm (CV group). An antiarrhythmic medication, including beta-blockers, propafenone and amiodarone, also in combinations, was also recorded. As the exact duration of the arrhythmia episodes was not possible to recollect, we only included the patients with persistent AF lasting from 2 to 24 weeks.

The P wave duration, was measured using LabSystem^{TM}Pro EP Recording System, Boston Scientific, where the ECG tracings allowed assessing the sinus P waves. The P wave duration was measured precisely in all leads at paper speed of 200 mm/s and enhancement 64-128. To avoid any influence of accidental measurement inaccuracies all the measurements were repeated 5 times and the mean value was presented as a result.

In patients with persistent form of atrial fibrillation the direct current cardioversion was performed as standard clinical procedure under general anesthesia using propofol 1 mg/kg and fentanyl 50 μg, administered intravenously. Single shock of 300 J was successful in all patients.

The study protocol was approved by the local Bioethical Committee at Wroclaw Medical University.

Statistical analysis

The statistical analysis was performed using the computer program STATISTICA v.13.3 (StatSoft, Inc., Tulsa, USA). P values less than 0.05 were considered significant.

For quantitative variables, basic descriptive statistics were calculated (M - average, SD - standard deviation, Me - median, Q1 - lower quartile, Q3 - upper quartile, Min - minimum value, Max - maximum value) and the compliance of their distributions with the theoretical normal distribution was checked using the Shapiro-Wilk's W test. Comparisons were performed with the Students' T test or Mann-Whitney U test for independent groups or Kruskal-Wallis ANOVA for multiple comparisons. Each categorical variables were presented as numbers and percentages. The comparisons were performed with the Chi-square test. The correlations between the studied parameters were performed using Spearman's rank correlation coefficient according to statistical properties of the data.

The receiver operational curve (ROC) was used to assess the ability of P wave duration to classify disease status. Based on the results of examination and receiver operating characteristic (ROC) analysis, a cut-off threshold for P wave duration was calculated for AF and CV groups.

Results:

The demographic and clinical characteristics of studied patients were presented in table 1.

Table 1. Clinical characteristics of the total population and the comparisons of two groups of studied patients.

	Total	AF	CV	p value
	N = 119 (100%)	N = 65 (54.6%)	N = 54 (45.4%)	
Mean age (years)	65.3 ± 9.4	65.0 ± 8.9	65.6 ± 10.1	0.712
Male/female	62/57	34/31	28/26	0.893
Comorbidities:				
HT	89 (74.8%)	48 (73.8%)	41 (75.9%)	0.962
DM	25 (21.0%)	12 (18.5%)	13 (24.1%)	0.601
CKD	9 (7.6%)	6 (9.2%)	3 (5.6%)	0.509
IHD	21 (17.6%)	12 (18.5%)	9 (16.7%)	0.989
HF	11 (9.2%)	3 (4.6%)	8 (14.8%)	0.065
K^+ (mmol/L)	4.45 ± 0.44	4.42 ± 0.43	4.49 ± 0.45	0.446
Glucose (mg/dL)	113.3 ± 29.4	108.0 ± 24.6	119.4 ± 33.4	**0.015**
Creatinine (mg/dL)	1.05 ± 0.28	1.01 ± 0.22	1.09 ± 0.34	0.340
Medicines:				
Propafenone	43 (36.1%)	19 (29.2%)	24 (44.4%)	0.126
Amiodarone	17 (14.3%)	9 (13.8%)	8 (14.8%)	0.910
Bisoprolol	22 (18.5%)	12 (18.5%)	10 (10.5%)	0.819
Metoprolol	86 (72.3%)	44 (67.7%)	42 (77.8%)	0.309
Mean P wave duration (ms)	151.5 ± 21.0	144.6 ± 17.2	159.9 ± 22.3	**<0.001**

Abbreviations legend: HT – arterial hypertension, DM – diabetes mellitus, CKD – chronic kidney disease, IHD – ischemic heart disease, HF – heart failure.

The P wave duration did differ significantly between the studied groups, lasting longer in patients with persistent form of arrhythmia. The same apply for fasting glucose concentration. The details are presented in Figure 1.

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Fig.1. Glucose level and average duration of P wave in groups of patients differing in the type of atrial fibrillation and the results of significance tests.

The P wave duration was significantly longer in patients with chronic kidney disease. The results are presented in Figure 2.

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Fig.2. The average duration of P wave in groups of patients differing in the presence of chronic kidney disease and the significance test result.

Moreover there was a weak but statistically significant correlation between the mean P wave duration and creatinine concentration. The results were depicted in Figure 3.

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Fig.3. Correlation diagram of average P wave duration with creatinine level and Spearman rank correlation coefficient and its 95% confidence interval.

The lower and upper limits of 95% CI are greater than zero, i.e. the correlation is positive and statistically significant ($p < 0.05$). The increase in creatinine concentration is accompanied by an increase in the duration of P wave.

However, no statistically significant relationship was observed between the dose of propafenone and the duration of the P wave. Spearman's rank correlation cohort rho does not differ significantly from zero (the lower and upper limits of the 95% confidence interval differ in sign, i.e. they contain 0; $p > 0.05$). This conclusion applies both to the entire studied group of patients and to the AF and CV groups separately.

There were no correlations between the P wave duration and propafenone treatment (dose) among all studied patients as well in AF and CV groups. The results are depicted in Figure 4.

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Figure 4. Correlation diagram of average P wave duration with creatinine level and Spearman's rank correlation coefficient and its 95% confidence interval.

The results of basic statistics of the duration of the P wave in groups of patients differing in the analyzed parameters and the results of significance tests are presented in table 2.

Table 2. Basic statistics of the average duration of the P wave in groups of patients differing in the analyzed parameters and the results of significance tests.

Variables	Mean P wave duration (ms)	Mean P wave duration (ms)	Mean P wave duration (ms)	P-value
	M ± *SD*	*Me* [*Q*1, *Q*3]	*Min* - *Max*	
Group:				**<0.001**
AF (n = 65)	144,6 ± 17,2	141 [133; 154]	116 - 196	
CV (n = 54)	159,9 ± 22,3	159 [139; 174]	126 - 216	
Gender:				0.273
Male (n = 62)	149,4 ± 20,2	147 [134; 162]	116 - 206	
Female (n = 57)	153,8 ± 21,8	145 [139; 167]	118 - 216	
Age (years):				0.193
[?] 65 (n = 52)	149,3 ± 21,7	141 [136; 161]	117 - 216	
> 65 (n = 67)	153,3 ± 20,5	150 [139; 167]	116 - 199	
HT:				**0.008**
Yes (n = 89)	154,4 ± 21,7	150 [139; 168]	116 - 216	
No (n = 30)	142,9 ± 16,2	139 [132; 151]	117 - 199	

Variables	Mean P wave duration (ms)	Mean P wave duration (ms)	Mean P wave duration (ms)	P-value
DM:				0.891
Yes (n = 25)	151,8 ± 21,9	145 [139; 172]	116 - 190	
No (n = 94)	151,5 ± 20,9	147 [138; 163]	117 - 216	
CKD:				**0.002**
Yes (n = 9)	170,6 ± 13,5	172 [163; 182]	150 - 185	
No (n = 110)	150,0 ± 20,8	143 [137; 162]	116 - 216	
IHD:				0.397
Yes (n = 21)	154,7 ± 22,8	151 [139; 177]	116 - 186	
No (n = 98)	150,9 ± 20,7	145 [137; 162]	117 - 216	
HF:				0.361
Yes (n = 11)	156,8 ± 24,7	160 [139; 182]	116 - 192	
No (n = 108)	151,0 ± 20,7	145 [137; 163]	117 - 216	
Propafenone:				0.519
Yes (n = 43)	153,2 ± 22,0	148 [139; 163]	117 - 216	
No (n = 76)	150,6 ± 20,5	145 [136; 164]	116 - 199	
Amiodarone:				0.796
Yes (n = 17)	150,3 ± 17,8	150 [141; 160]	116 - 182	
No (n = 102)	151,7 ± 21,6	144 [137; 167]	117 - 216	
Metoprolol:				0.974
Yes (n = 86)	151,2 ± 20,9	148 [138; 163]	116 - 216	
No (n = 33)	152,3 ± 21,7	141 [137; 170]	123 - 198	
Bisoprolol:				0.453
Yes (n = 22)	147,6 ± 17,7	144 [139; 156]	125 - 199	
No (n = 97)	152,4 ± 21,7	148 [138; 167]	116 - 216	

Abbreviations legend: HT – arterial hypertension, DM – diabetes mellitus, CKD – chronic kidney disease, IHD – ischemic heart disease, HF – heart failure.

In one-way analysis it turned out that the duration of the P wave has a statistically significant relationship with the diagnosis (AF = 0, CV = 1) as well as hypertension and chronic kidney disease. Due to the possibility of a strong correlation between these parameters, a multifactorial (progressive stepwise) regression analysis was performed. As a result, the following model was obtained:

$$Mean\ P\ wave\ duration = 120.3 + 15.8 * CV + 20.2 * CKD + 9.0 * HT \pm 18.5$$

The factors (stimulants) of longer duration of the P wave turned out to be: belonging to the CV group, the presence of chronic kidney disease and hypertension. All structural parameters of the model are statistically significant ($p < 0.0001$): $F(3, 115) = 12.6$; $p < 0.001$.

The duration of the P wave can be regarded as a parameter enabling classification of patients into the CV or AF group. Analysis of the ROC curve (Receiver Operating Characteristic curve) showed that for the cut-off value P wave duration> 148 ms the diagnostic sensitivity of the test was 67.7%, specificity 66.7% and the area under the ROC curve, AUC = 0.700. This is not a sensational result, but the lower confidence limit for AUC is 0.609 and is greater than 0.5 - this indicates the diagnostic usefulness of this parameter. According to the literature, if the AUC is in the range of 0.7 to 0.8, the classifier is satisfactory. The graphic presentation was depicted in Figure 5.

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Fig. 5. ROC curve for the duration of the P wave; cut-off value between patients from the CV group and patients from the AF group; sensitivity and specificity of the test and area under the ROC curve and its 95% confidence interval.

Discussion:

The duration of the P wave is a result of the conduction velocity in the atrial working myocardium and the distance the electrical activation has to travel. Functional and structural changes in the atrial muscle affect both of these parameters - they slow down conduction velocity and extend the way to travel due to the enlargement of the atria. This results in an extension of the P wave duration and a change in its morphology. The same changes in structure and function are responsible for generating atrial arrhythmias including atrial fibrillation [8]. Additionally, the ongoing arrhythmia leads to progression of the above mentioned changes. In particular the enlargement of left atrium is clearly associated with an increase in filling pressure of the left ventricle and probably dependent on the ventricular rate [12]. Data on the effect of AF on muscle conduction are more scarce and equivocal [13].

The main result of our study is to show a longer duration of the P wave in patients with average long-term persistent atrial fibrillation compared to patients with paroxysmal arrhythmia and sinus rhythm at the time of the study. The degree of this elongation (about 10%) of the P wave duration is not only statistically but also clinically significant. It should be emphasized that the P waves measured by us in both groups markedly exceed the normal values of 120 ms (144.6 vs 159.9 ms, respectively). Similar comparisons are not numerous in the available literature [14, 15]. As our subgroups of patients suffering from paroxysmal and persistent AF are comparable according to age, gender distribution, comorbidities and anti-arrhythmic medication, it indicates that this additional prolongation is caused only by the presence of the prolonged episodes of arrhythmia. Our measurements were not performed immediately after the cardioversion shock, so the influence of direct current can be skipped. Additionally the direct current flow during cardioversion had little or no effect on the P wave duration in one small study immediately after the procedure and on the next day [16].

Even if diabetic patients were not frequently presented in our studied group there was a noticeable difference between diabetics and non-diabetics in terms of P wave duration. Those with DM were observed to have a longer P wave than participants without it. This is in line with the other clinical observations even the direct evidence lacks in human. Diabetes is presumed to be a risk factor for atrial fibrillation and the topic has been reviewed quite often. A meta-analysis of different cohort and case control studies investigating the correlation of DM and AF, showed that individuals with DM had a 40% greater risk of AF compared to unaffected individuals [17]. There is only sparse literature to be found about DM leading to electrical changes of the atrial substrate [18]. In an experimental setting of DM it was associated with increased atrial fibrosis, interatrial conduction delay and greater inducibility of AF [19]. Another animal study confirmed those results with additional interesting observations of either P wave prolongation in diabetic rats without left atrial enlargement, for which the authors accounted diabetic changes in the gap junction protein Cx [20]. Similar outcomes were obtained in patients with impaired fasting glucose leading to significantly prolonged interatrial conduction times and consecutive decrease left atrial emptying volume and fraction [21].

In another subgroup of our patients the chronic kidney disease was found to be a predictor of longer P wave duration. In the literature some researches made already the association between maximum P wave duration and exacerbation of the renal condition until the defined end points of hemodialysis, death or a specified decline in estimated glomerular filtration rate [22. 23]. Based on our results it could be assumed, that a vice versa influence of CKD on the P wave duration is occurring as well, possibly because of a simple fluid overload. Referring to the patients included in our study, only a small number of 9 (7.6%) patients presented with CKD as a comorbidity but it was discovered to be a statistically significantly related to the P wave duration. This needs further investigation in other studies, not distorted by the small number of CKD patients. Atrial fibrillation is frequently described together with a renal dysfunction but mainly as a preceding comorbidity but no relation was found for CKD being the reason of AF. Nevertheless our results indicate such possibility making the subject worth to be studied.

The anti-arrhythmic medication influences the electrophysiological properties on the working myocardium, in particular the conduction speed and refractory period which could influence the P wave duration. The results of our study do not support such concept. Amiodarone is a class III antiarrhythmic agent acting mainly as potassium channel blocker, characterized by prolongation of the refractory period and atrial repolarization. It has been shown to be effective in maintaining sinus rhythm and preventing arrhythmia episodes in patients with paroxysmal atrial fibrillations. Even if in one small study researchers described the amiodarone-related increase in P wave duration, this was a small experimental animal study and the conditions were not comparable in sinus rhythm in human, present in our study [24]. The relationship between P wave duration and amiodarone administration was similarly negated in a study conducted by Sasaki et al. [25].

In contrast to amiodarone the treatment with sodium channel blocker could theoretically influence the P wave duration. Propafenone is an IC class agent which blocs the fast sodium channels, slowing down the conduction velocity in the working myocardium. According to literature data there is no direct relationship between the dose of propafenone and the duration of the P wave, however the same study confirms a weak correlation between the treatment with propafenone and the elongation of the P wave duration [26]. Our data do not confirm this finding. One should however emphasize that our propafenone treated patients' group was not large.

Based on our results the theoretical model resulting from ROC curves indicated the estimated P wave duration differentiating patients between sinus rhythm and persistent atrial fibrillation groups. In the literature, this approach has not been presented so far, so our value of P wave duration - 148 ms can only be referred to studies indicating the importance of this parameter in the prediction of sinus rhythm maintenance after electrical cardioversion. In 1999 Aytemir and co-authors investigated the P wave signal-averaged ECG in 73 patients after successful cardioversion. During 6 months follow-up period the recurrence of AF was observed in 31 patients and in 42 patients sinus rhythm was maintained. The researchers found no difference between the groups according to gender, age, presence of organic heart disease, left atrial diameter, left ventricular ejection fraction, use of antiarrhythmic drug, and duration of atrial fibrillation. The filtered P wave duration was statistically longer in patients with recurrence of atrial fibrillation 138.4 vs. 112.5 ms. A filtered P wave duration of 128 ms was had a sensitivity of 70% and specificity of 76% for the detection of recurrence of atrial fibrillation [27]. On the other hand in the study of Perzanowski et al. the maximum duration of the P wave did not differentiate patients who remained in sinus rhythm or experienced a recurrence of arrhythmia (142 vs 145 ms; p=n.s.) [28]. As the authors did not mention the methodology of P wave duration measurements it should be assumed that they used simple standard 12 lead ECG without any more precise equipment. This lack of precision could be the cause of their results. In the study of Gonna and co-workers a 12-lead ECG was recorded after electrical cardioversion for persistent AF in 77 patients and repeated after 1 month. Compared with the sinus rhythm group, the one with recurrent AF had more patients with P wave duration exceeding 142 ms. Using a cutoff of <142 ms for P wave duration the authors showed a sensitivity of 64.6% and specificity of 62.1% for sinus rhythm maintenance. In multiple regression analysis the P wave duration longer than 142 ms was the only independent predictor of AF recurrence [29]. The above-mentioned considerations indicate unequivocally that the prolongation of the P wave is clearly a risk factor for paroxysm of atrial fibrillation and more advanced stages of the arrhythmia, which is in line in our results. Moreover in different settings we produced the evidence which supports the previous findings. According to the higher values of the P wave duration obtained by us, it should be remembered that the precise methodology used in our study is qualitatively different from that of other researchers [28, 29]. This is a reason that already a few years ago we confirmed the lack of P wave dispersion, assessed in some of the above papers, which is related to the inaccuracy of the measurement [30].

In summary the ongoing atrial fibrillation in form of moderately long persistent arrhythmia influences negatively the structural and functional atrial remodeling. This occurs independently from age and gender, sort of anti-arrhythmic treatment but can be slightly related to some comorbidities.

Study limitations:

An important limitation of our study is its single-center design and relatively small study group. In addition, this is not a prospective clinical study indicating the relationship between ECG parameter and long term prognosis. As our measurement method using the electrophysiological recording system is extremely precise we are aware, that our results could not be comparable directly to the results of other authors. We've already mentioned, the duration of persistent form of the arrhythmia could not be exactly estimated. Because our hypothesis is the prolongation of the duration of the P wave is mainly related to atrial fibrillation itself, it should be assumed as the main limitation of our study, even if the literature data contradict the correlation between the arrhythmia duration and P wave prolongation [16].

Conclusions:

1. The persistent atrial fibrillation shows prolongation of the P wave duration over the paroxysmal form of the arrhythmia, independently to age, gender and anti-arrhythmic medication.
2. The prolongation of the P wave related to persistent arrhythmia should force the physicians to earlier restoration of the sinus rhythm in order to its more successful long term maintenance.

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