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Researching the Presence of P Dispersion Among Children of Adult Patients with Idiopathic Atrial Fibrillation

İdiyopatik Atriyal Fibrilasyonlu Erşkinlerin Çocuklarında P Dalga Dispersiyonu Varlığının Değerlendirilmesi

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ABSTRACT Objective: Interatrial and intraatrial conduction problems were detected in individiuals with atrial fibrillation (AF). Genetic studies in AF patients has been suggested that atrial and ventricular arrhythmias are both associated with common genes. The conduction patterns in atrial arrhythmias are defined by P-wave dispersion (PWD) index. **Material and Methods:** Twenty six children of 16 idiopathic AF patients and 29 healthy children from 29 different families were enrolled in the study. One group had a family history of idiopathic AF, in one of the parents. Electrocardiography findings [heart rate, rhythm, maximum (max) and minimum (min) durations of P wave, QT, QTc intervals, and also dispersions] were recorded. Electronic ruler measurement mean values were calculated from 3 subsequent cycles of the DII derivation. **Results:** Comparing the factors of P_{min}, QRS, QT_{max}, QT_{min}, QTd, QTc_{max}, QTc_{min}, QTc dispersion and J point-T peak time, no significant difference was detected between the two groups ($p>0.05$). P_{max} and PWD (108.4±11 ms versus 94.2±9.6 ms and 54±11 ms versus 43±9 ms $p<0.0001$) were found to be significantly higher in the study group, respectively, whereas PR interval time was significantly higher in the control group (129±17 ms versus 143±18 ms $p=0.001$). **Conclusion:** PWD can be used to determine the likelihood of AF in the presymptomatic stage. Further studies are needed including long-term outcomes of healthy children with idiopathic AF family history, associated with the development of AF in adulthood.

Keywords: Atrial fibrillation; child; electrocardiography

ÖZET Amaç: Sinüs uyarılarının intraatriyal ve interatriyal ileti sürelerinde uzama atriyal fibrilasyon (AF) bulunan hastalarda gözlenen temel elektrofizyolojik bozukluklardandır. Genetik çalışmalarda idiyopatik atriyal ve ventriküler aritmilerin benzer genlerle ilişkisi saptanmıştır. Atriyal aritmili hastalardaki iletim kalıbı, P dalga dispersiyonu [P-wave dispersion (PWD)] adı verilen indeksle değerlendirilmektedir. **Gereç ve Yöntemler:** Çalışmaya 16 erişkin idiyopatik AF hastasının 26 sağlıklı çocuğu ve 29 farklı aileden 29 sağlıklı çocuk dâhil edildi. Ebeveynlerinden birinde idiyopatik AF olan çocuklar ve aile öyküsünde kalp hastalığı bulunmayan sağlıklı çocuklarda elektrokardiyografi bulguları [kalp hızı, ritim, P dalgası, QT ve QTc intervallerinin maksimum (maks) ve minimum (min) süreleri, QT, QTc ve PWD] kaydedildi. Ölçümler D II derivasyonundan elde edilerek bilgisayar ortamında elektronik hassas cetvel ile üç ardışık derivasyon ölçümlerinin ortalaması alındı. **Bulgular:** Çalışma grubunda sırasıyla P_{maks}ve PWD daha yüksek (108,4±11 ms; 94,2±9,6 ms, 54±11 ms; 43±9 ms $p<0,0001$), kontrol grubunda ise PR interval zamanı (129±17; 143±18, $p=0,001$) daha yüksek bulundu. P_{min}, QRS süresi, QT_{maks}, QT_{min}, QT dispersiyonu, QTc_{maks}, QTc_{min}, QTc dispersiyonu ve J noktası-T pik zamanı faktörlerinin karşılaştırılması ile iki grup arasında anlamlı bir fark saptanmadı ($p>0,05$). **Sonuç:** PWD, presemptomatik evredeki AF olasılığını belirlemek için kullanılabilir. Aile öyküsünde idiyopatik AF olan çocukların erişkin dönemde AF geliştirme açısından uzun dönemde izlenmesi ve sonuçlarını içeren yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Atriyal fibrilasyon; çocuk; elektrokardiyografi

Atrial fibrillation (AF) is a type of arrhythmia which is rarely seen in the pediatric population. The main electrophysiologic disorders encountered in AF patients are prolonged interatrial and intraatrial conductions.[1-3] Lone or idiopathic AF which occurs with unknown etiology is seen in 2%-16% of pediatric and adult patients. It has been suggested that AF is associated with genetic factors in these cases. Several

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electrocardiograph (ECG) findings are expected to be in children of AF patients by reason of genetic factors in AF with unknown etiology.

In recent studies, P-wave dispersion (PWD) has been observed in patients with AF. PWD is a new and simple electrocardiographic parameter that has been reported to be associated with inhomogenous and discontinuous propagation of sinus impulses.[4] PWD is defined as the difference between the widest and the narrowest P wave duration from the 12 ECG leads.[4] Besides AF, PWD is increased by atrial strain consisting of pressure or volume load, electrolyte abnormalities and increased sympathetic activity.[4-9]

Previously, PWD has been studied in hypertension, obesity, insulin resistance, Diabetes mellitus, anorexia nervosa, asthma, acute romatic fever, migraine attacks, childhood obstructive sleep apnea syndrome, inflammatory bowel disease, coronary artery disease, mitral valve prolapse, congenital heart disease which undergone cardiac surgery, various cardiac and non-cardiac diseases as well as for the healthy population in childhood.[10-20] In many clinical conditions, it may determine the risk of AF with relatively high sensitivity and specificity.

In healthy students PWD was influenced by gender, body mass index and heart rate. In a study, which was conducted among students who were doing regular sport activities, PWD was determined to be higher in boys than in girls.[21]

The QT interval reflects the total duration of ventricular depolarization and repolarization. The extended QT interval is also a simple indicator of ventricular myocardial depolarization and repolarization abnormalities.[22] Changes in the QT interval are also called QTd and it is suggested that such changes in the QT interval show the regional differences in ventricular repolarization.[23,24]

This study was planned considering similar genetic predispositions causing both atrial and ventricular arrhythmias. It was thought that P and QT dispersion times may be longer in children of adult idiopathic AF cases.

The aim of this study is to evaluate PWD and QTd whether to predict the risk of atrial and ventricular arrhythmias using a non-invasive ECG method in children of those patients with idiopathic AF.

MATERIAL AND METHODS

The children of 16 patients with idiopathic AF who were being followed by Türkiye Yüksek İhtisas Hospital cardiology clinics were enrolled in this study. Underlying etiology of this group was explored. The age range of the AF cases were less than 55 years. Valvular heart disease, occult cardiac pathologies such as hypertension or ischaemic heart disease, endocrine causes were explored in these patients and any reason could not be obviously identified.

The study group consisted of 26 healthy children of 16 patients who had idiopathic AF. The control group consisted of 29 children from 29 different families who had no chronic disease or family history of AF. Both groups had similar age and gender characteristics. Control group were randomly selected within patients who had been referred to Dr. Sami Ulus Obsterics and Paediatrics Research and Training Hospital due to the presence of innocent cardiac murmur. The study was conducted between January 2013 and April 2013. Informed consent forms were obtained from both the study and control groups.

The study was performed in accordance with the Declaration of Helsinki for Human Research. The study was approved by the ethics committee of Zekai Tahir Burak Women's Health Training and Research Hospital on 11.12.2012 with decision no: 77.

Criteria for inclusion to the study were;

- Being under the age of 18 years
- Being the children of an AF patient (for the study group)
- Not having any additional cardiac abnormalities or under medical treatment that can affect ECG
- Obtaining informed consent from their parents

Certain factors involving their age, gender, weight, height, the presence of close relative marriage, a family history of sudden infant death syndrome or sudden cardiac death and existence of AF in the family were all recorded. Palpitations, chest pain,

syncope with unknown etiology, a history of chest tightness were all examined in both the study and control groups to determine any cardiac symptoms.

Physical examination results were recorded along with the weight and height of the participants. Standart beam scale and height board were used to evaluate the anthropometric measurements (GL200, G-tech International CO, LTD; Turkey).

A 12 lead ECG was used to examine all the participants with a 6-channeled ECG device. All measurements were done by the same staff at similar conditions with the child lying down, after a resting period of ten minutes. All ECG records were evaluated by a pediatric resident together with a senior pediatric cardiology specialist. The ECG records were first assessed visually and then computerized. The MB ruler 1.52 programme was used for the measurements. The electronic ruler measurements mean values were calculated from 3 subsequent cycles of the same derivation. The ruler measurements were found to be more reliable than visual method in previous studies.

The control group consisted of children who had no cardiac or chronic disease, had normal growth and neuromotor development, had been examined for innocent cardiac murmur and no pathological signs had been observed. The age and gender of the control group were similar to those of the study group.

ECG evaluation: 12-lead surface ECG was performed with an electrocardiograph (Nihon Kohden ECG, 1250K, Tokyo, Japan). Recordings were taken at a calibration of 10 mm/mV and the paper speed was 25 mm/s. The duration between J point and T peak, the minimum and maximum durations of P wave (P_{min} and P_{max}), PWD, the minimum and maximum durations and dispersions of QT and OTc of 12 derivations were determined. The distance from the beginning of the Q-wave to the last point where the T-wave returned to isoelectric line is defined as the QT interval. If U-waves are present, the narrowest points between the T- and U-waves are accepted as the end of the T-wave. QT dispersion is defined as the difference between the widest QT interval (QT_{max}) and the narrowest QT interval (QT_{min}), as milliseconds. QT_c intervals (milliseconds) are calculated using Bazett's formula (QT_c= QT interval/RR interval). The rhythm, axis, mean heart rate, duration of PR interval, QRS duration, duration between J point and T peak, ST segment and T wave were all evaluated from DII derivation. The P-wave was defined between the duration of the positive and negative deflections, from the beginning of the junction between the isoelectric line to the offset of the P-wave. Maximum P-wave duration (P_{max}) interval was the widest P-wave value, minimum P-wave duration (P_{min}) interval was the narrowest, each of them measured. PWD was calculated, the difference between P_{max} and P_{min} (as milliseconds). All ECG records were scanned with a 300 dots per inch (dpi) resolutioned computer. They were opened with an upsized x400 microsoft office picture manager programme then measured with an electronic ruler using the MB ruler programme. The visual and computer program measurements were calculated and then computer measurements were selected.

STATISTICAL ANALYSIS

IBM SPSS for Windows version 21.0 was used to analyze the data. The numeric variable was presented as mean±standard deviation and mean (minimum-maximum). The categorical variable was presented as number and percentage. The chi-square test was used to show the differences concerning categorical variables between the groups. The Shapiro-Wilk test was used to show the normality of numeric variable and the Levene test for homoscedasticity.

The differences between independent variables concerning numeric variables were examined with T test in cases of parametric test assumption. Mann-Whitney U test was used in cases with non-parametric test assumption. The value of significance was $p<0.05$.

RESULTS

The study group was consisted of 26 children (47%) and the control group consisted of 29 children (53%). The demographics of the participants are shown in Table 1. The mean age of the study group was 104±62 months. There were 12 boys (46.2%) and 14 girls (53.8%) in the study group. The mean age of the control group was 99±50 months. In the control group there were 17 males (58.6%) and 12 females (41.4%). There was no relationship concerning age

TABLE 1: Participants' demographic features.

	Control	Study group	p value
Number of cases	29	26	
Age (months)	99±50	104±62	0.758
Gender			0.513
Female	12	14	
Male	17	12	
Anthropometric measures			
Weight (kg)	30.3±14.7	31±18.3	0.884
Height (cm)	128.1±26.4	127.6±30.4	0.954
Type of atrial fibrillation			
Paroxysmal	-	24	
Paroxysmal fibro-flutter	-	1	
Paroxysmal fibrillation-SVT	-	1	
Consangionuity			
Second degree	1	5	
Distant	-	3	
No	28	18	
Symptom			
Palpitation	-	1	
chest pain	8	1	0.093
Syncope	-	1	
Tightness in chest	2	-	
Normal	19	23	
Physical examination outcomes			**<0.0001**
Murmur	2	4	
Pectus excavatum	-	1	
Normal	-	21	

SVT: Supraventricular tachycardia.

Values are presented as mean±standart deviation. The mean difference is significant at the 0.05 level. Significant p values are shown in bold.

and gender distribution between the study and control groups respectively (p=0.758, p=0.513).

The mean weight was 31±18.2 kg in the study group and 30.3±14.7 kg in the control group. The mean height was 127.6±30.4 in the study group and 128.1±26.4 cm in the control group. There was no relationship as far as weight and height were concerned between the study and control groups respectively (p=0.884, p=0.954).

The mean P_{max} was 108.42±11.172 ms, the mean P_{min} was 54.27±5.568 ms and the mean PWD was 54.08±11.805 ms in the study group. The mean duration of PR interval was 129.42±17.732 ms, the mean duration of QRS 56.12±12.694 ms, the mean QT_{max} 353.88±43.305 ms, the mean QT_{min} 296.04±38.989 ms, the mean QTd 57.77±19.402 ms, the mean QTc_{max} 434.42±16.209 ms, the mean QT_c min 363.12±021.737 ms, the mean QT_c dispersion 71.31±19.417 ms and the mean duration between J point and T peak was 215.62±29.570 ms.

The mean P_{max} was 94.24±9.676 ms, the mean P_{min} 51.21±6.126 ms and the mean PWD 43.03±9.682 ms in the control group. The mean duration of PR interval was 143.31±18.567 ms, the mean duration of QRS 63.79±17.131 ms, the mean QT_{max} 350.34±033.274 ms, the mean QT_{min} 290.48±26.091 ms, the mean QTd 59.86±18.136 ms, the mean QTc_{max} 440.83±17.740 ms, the mean QT_c min 359.62±23.067 ms, the mean QT_c dispersion 81.28±20.927 ms and the mean duration between J

point and T peak was 209.03±28.655 ms. P_{max} duration and PWD were found to be higher in the study group ($p<0.0001$). The duration of PR interval was found to be higher in the control group ($p<0.0001$). There was no relationship between the two groups concerning of P_{min}, QRS duration, QT_{max}, QT_{min}, QTd, QTc_{max}, QTc_{min}, QTc dispersion or the duration between J point and T peak ($p>0.05$). The ECG changes of all participants are shown in Table 2.

DISCUSSION

AF is a kind of arrhythmia which is rarely seen in the pediatric population. AF is activated in an irregular and asynchronous manner, and the velocity of the rhythm is 400-700 beats/minute. It is seen in children who have genetic syndromes such as Wolff-Parkinson-White or short QT as well as in children who have been operated for atrium diseases such as total cava-pulmonary anastomosis or atrial switch.[25-27] There is a risk of AF in hyperthyroidism, rheumatic mitral valve disease, hypertrophic and dilated cardiomyopathy, myocarditis or digoxin intoxication.

PWD is the difference between the maximum and minimum P wave durations which are recorded from different ECG derivations.[4] P wave duration and PWD are used to determine the rate of atrial impulse. PWD and P_{max} reflect atrial muscle activity and basically depend on the amount of tissue. It is a simple ECG result which is used to determine the intraatrial or interatrial conduction time and the propagation of non-homogenous sinus impulses in the atriums prone to fibrillation. PWD is increased by atrial strain which is consisting of pressure or volume load, electrolyte abnormalities and increased sympathetic activity.[4-9] Non-homogenous and discontinuous propagation impulses in patients with atrial arrhythmia is a valuable parameter in order to predict the risk of AF.[1]

QT interval and corrected QT are used to evaluate ventricular repolarization in clinical applications. The repolarization abnormalities cause an increase in QT dispersion in patients with cardiac problems. QTd is a simple but directing criteria to evaluate the repolarization abnormalities. An increase in QT dispersion demonstrates non-uniform ventricular

TABLE 2: The ECG changes of all participants.

	Control	Study group	p value
Number of cases	29	26	
P_{max} (ms)	94.2±9.6	108.4±11	<0.0001
P_{min} (ms)	51±6	54.2±5	0.298
P wave dispersion (ms)	43±9	54±11	<0.0001
PR duration (ms)	143±18	129±17	=0.001
QRS duration (ms)	63±17	56±12	0.019
QT_{max} (ms)	350±33	353±43	0.83
QT_{min} (ms)	290±26	296±38	0.486
QT dispersion (ms)	59±18	57±19	0.493
QTc-maximum (ms)	440±17	434±16	0.058
QTc-minimum (ms)	359±23	363±21	0.73
QTc dispersion (ms)	81±20	71±19	0.045
Jpoint-Tpeak interval (ms)	209±28	215±29	0.339
Mean heart rate (beats/minute)	97±18	99±26	0.74
Sinus rhythm	27	18	
Sinus arhythmia	-	4	
Sinus tachycardia	2	4	
Axis	0 - +90	0 - +90	>0.05

ms: Millisecond; QT_c: Corrected QT.

Values are presented as mean±standart deviation. The mean difference is significant at the 0.05 level. Significant p values are shown in bold.

repolarization and this situation may cause malign ventricular arrhythmia.

P wave duration, PWD, QT and QT_c dispersion were evaluated by surface ECG in this prospective and clinical laboratory study which compares the ECG findings of the children of AF patients with those of the healthy population. In the present study, we aim to research the electrocardiographic changes that represent atrial propagation and ventricular repolarization abnormalities in children of idiopathic AF patients. An automated and measured system of ECG was used to record and investigate the data.

PWD and P_{max} which indicate a risk of AF were observed to be higher in the otherwise healthy children of AF patients ($p<0.0001$). To the best of our knowledge there are no studies evaluating the ECG aspects of children of AF patients to determine atrial and ventricular abnormalities.

Coronary atherosclerosis is an important problem among adults in Turkey. Coronary heart disease is the principal cause in the etiology of considering the occurrence of AF. The etiology of AF in the parents of our study patients likely to be genetical, in relation to no reason was found when searching for possible etiologies. Nevertheless, the P wave abnormalities of children of these families show that genetic etiology may cause the occurrence of AF. Long-term and prospective studies are needed to determine the exact causes. PWD is an early and non-invasive identification method of coronary atherosclerosis which begins in early childhood which is able to predict the risk of AF. In fact there is no limit value for all ages and there is no mean PWD value for early childhood. The relationship between AF and coronary atherosclerosis is an unknown quality. The PWD values of children with and without hyperlipidemia might be evaluated and indeed a mean PWD value may be calculated in the future so that hyperlipidemic patients will be able to be followed with PWD controls. Therefore there are studies investigating the relation of antihypertensive treatment and PWD values in adults. PWD values can be used as a non-invasive method to follow changes in rhythm in children with hypertension, obesity or hyperlipidemia.[28]

There have been several studies in adults with chronic disease which have investigated atrial and ventricular abnormalities by using ECG. On the other hand, few studies were about this subject in children. Although there have been several adult studies concerning hypertension, metabolic syndrome and PWD value, there have been few in children. Dilaveris et al. found that morphological abnormality of P wave was rare but that wide P wave duration was more common in their study which investigated the prevalence of interatrial block by analysing P wave morphology and duration in healthy children.[29] In studies P wave duration ≥110 ms in adult and ≥90 ms in children indicates abnormal P wave and interatrial block. Akyuz et al. studied the effect of low birth weight with atrial conduction and ventricular repolarization. They compared PWD and the dispersion of QT and QT_c between low birth weight and normal birth weight infants but found no relationship.[30] Chavez et al. studied the relationship between AF and hypertension. PWD was found to be higher in hypertensive and prehypertensive children than in normotensives ($p<0.001$).[31] A relationship was found between PWD and left ventricle muscle index in hypertensive patients. Short term mortality and arrhythmia were studied by Amoozgar et al. using PWD to check atrial conduction in asphyxiated newborns without congenital disorders.[32] PWD was found to be higher depending on the stage of asphyxia. Nevertheless there was no relationship between short term mortality, arrhythmia and troponin T levels.

Although the pathophysiology of neurocardiogenic syncope has not been fully explained, there are studies suggesting that cardiac autonomic instability is responsible. Cardiac autonomic tone may alter the duration of the P wave by affecting atrial conduction velocity. In a study conducted in the adolescent group, PWD was found higher in neurocardiogenic syncope group than the healthy control group.[33]

PWD and QTd were prolonged in children with beta thalassemia major. This indicates cardiac autonomic dysfunction. Moreover, positive correlation with ferritin level and echocardiographic data of cardiac involvement was detected.[34]

Hypoxia, hypercapnia, autonomic dysfunction, atrial streching, negative intra-thoracic pressure effect, and all conditions causing inflammation can be an independent risk factor for atrial arrhythmias. PWD and QTd may vary depending on the methods used in the treatment of congenital anomalies of atria and ventricles. When transcatheter correction was applied in cases with secundum ASD, there was a decrease in PWD in the post-procedure period, since there was no scar tissue due to surgery and no bypass was performed.[35]

Psoriasis is a multi-system disease with chronic inflammation and cardiovascular morbidity. There are studies showing that there is a relationship between psoriasis and cardiovascular risk factors in adults. Psoriasis and atherosclerosis are thought to have similar inflammatory mechanisms. In a study of children considering the pathophysiology of inflammation, P_{max} and PWD were found higher in patients with psoriasis than in the healthy control group.[36]

There have also been genetic studies. Atrial fibrillation is the most common form of arrhythmia in adults. Although the incidence of familial forms is not exactly known it is estimated to be around 30%. Gene mutations of KCNE2, KCNJ2, KCNA5, KCNH2 were found in few familial AF cases. These genes compose the proteins which organize the channels transporting K^+ ions inside and outside of cell membranes. The mutation of these genes increases the channel activation then causes the transportation of K^+ ions to change which result in arrhythmia. In several cases of, AF the etiology has not been determined yet it is believed that genetic risks are responsible. Studies to determine the mutant genes are ongoing.[37,38]

CONCLUSION

The present study has shown that PWD should be used as a non-invasive method to determine the real stage of risk of AF in those patients who would appear to be at high risk. More importantly, a rhythm disorder such as AF can be detected in the presymptomatic period, and symptoms may be prevented or delayed. According to our findings, although the patient group was asymptomatic and no arrhythmias were detected in their surface ECG, due to idiopathic AF in family history, these cases should be followed to see long-term results and new studies should be planned including new cases. PWD does not have an average value in a healthy group of children. ECG investigations in the healthy children can identify a PWD upper and lower value that may be specific to each age group. So that a percentile chart specific to age and population may be achieved. The risk for all ages can be pre-calculated through these charts.

LIMITATIONS

Inadequate number of cases included in our study because of the low number of patients with idiopathic AF. Long term follow up was required for a comprehensive evaluation, contrary to our study. The fact that most of the individuals with idiopathic AF are of advanced age and the distribution of children in the adult age group were the limitations of the present study. Further studies are required including more participants that can be verified by genetic analysis. These studies will shed light on the elucidation of the atrial and ventricular rhythm genetics.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Selmin Karademir, Serkan Bilge Koca;* ***Design:*** *Selmin Karademir, Serkan Bilge Koca;* ***Control/Supervision:*** *Selmin Karademir, Serkan Bilge Koca;* ***Data Collection and/or Processing:*** *Süleyman Kalaycı, Serkan Bilge Koca;* ***Analysis and/or Interpretation:*** *Serkan Bilge Koca;* ***Literature Review:*** *Serkan Bilge Koca, Senem Özgür;* ***Writing the Article:*** *Senem Özgür, Serkan Bilge Koca;* ***Critical Review:*** *Senem Özgür, Serkan Bilge Koca;* ***References and Fundings:*** *Serkan Bilge Koca;* ***Materials:*** *Serkan Bilge Koca, Süleyman Kalaycı.*

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