Importance of P-Wave Indices in a Sample of Iraqi Type 2 Diabetic Patients

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Abstract
Background: Diabetes mellitus has a negative impact on the cardiovascular system; P-wave indices were considered to reflect the discontinuous and inhomogeneous propagation of sinus impulses and prolongation of atrial conduction time.
Objectives: to know importance of P-wave indices and significant of its use for prediction and evaluation of diabetic complication in type 2 diabetics.
Methods and Results: A case control study, Dec. 2011, on diabetics (n=88) and healthy relatives (n= 70) were conducted in the NDC. Comparing both groups for age, sex, resting heart rate and BMI revealed insignificant differences, $P > 0.05$. P-wave indices of diabetics shown absence of any correlation with the age, duration of diabetes, FPG, BMI, resting heart rate and HDL; But, it shown weak correlation with HbA1c, Serum cholesterol, serum triglycerides and LDL. P-wave indices show significant higher values in diabetics than in healthy subjects, $P < 0.05$, except for the P_{min}, $P > 0.05$.
Conclusions: P-wave indices (P_{mean}, P_{max}, and Pd) were significantly higher in diabetics than the healthy individuals. P-wave indices of diabetics have no effect on gender, age and BMI; but, have weak correlation with HbA1c, Serum cholesterol, serum triglycerides and LDL.

Keywords: Type 2 diabetes mellitus, P-wave indices, atrial fibrillation.
Abbreviations:ECG = electrocardiography, WHO = world health organization, IDF = international diabetes federation, NCEP/ATP III = National Cholesterol Education Program/Adult Treatment Panel III, NDC = national diabetes center, BMI = body mass index, AF = atrial fibrillation, Pd = P-wave dispersion, DM = diabetes mellitus, PAF = paroxysmal Atrial Fibrillation

Introduction

The pathological mechanisms related to initiation and maintenance of atrial fibrillation (AF) in patients with diabetes mellitus (DM) has not been well described. In diabetic cases it is thought that myocardial ischemia as a result of coronary microcirculation disorders or metabolic stress on atrium can play a role. Hypertension and coronary artery diseases, which are important factors in development of AF, often accompany DM [1]. Diabetic autonomic neuropathy (DAN) is a frequent complication of diabetes mellitus and has a negative impact on the cardiovascular system; such as, atrial fibrillation (AF) which is the most common sustained arrhythmia [2].

There are no data about the occurrence of paroxysmal atrial fibrillation (PAF) in the population with DAN [2]. It was shown in epidemiological studies that the rate of development of AF in diabetic cases is higher than normal cases [3].

Nevertheless, a consensus regarding P-wave indices, P-wave dispersion (Pd) values, distinguishing normal patients from high-risk patients, is lacking. Various research groups have included control subjects with different clinical characteristics [4].

Cardiovascular risk factors, like obesity, hypertension, coronary artery disease, valvular disease, and diastolic dysfunction, were all suggested to influence the Pd values. Nonetheless, the influences of demographic parameters such as gender, age, and body mass index (BMI) on P-wave parameters remain to be determined [4].

P-wave dispersion (Pd) is defined as the difference between the minimum (P_{min}) and

maximum (P_{max}) P-wave durations on standard 12-lead electrocardiography (ECG). Pd is a measure of heterogeneity of atrial refractoriness and prolongation of Pd shows the intra-atrial and inter-atrial non-uniform conduction [5]. Pd is considered to reflect the discontinuous and inhomogeneous propagation of sinus impulses and prolongation of atrial conduction time [6].

We tried in this study to shed light on the importance of P-wave indices and significant of its use for prediction and evaluation of diabetic complication in Iraqi sample of type 2 diabetic patients.

Patients and Methods

Ethical approval

All patients were informed about the aim and the suspected benefit of the study before obtaining their agreements for participation according to the medical research and ethical regulations, thus an oral consent was taken from all enrolled participants.

All the medical research ethics rules and instructions adopted in National Diabetes Center (NDC) regarding patient's privacy, humanity and security; as well as the medical research, laboratory data and investigation results were strictly considered throughout all the steps of study.

Setting

A case control study was conducted, Dec. 2011, on Iraqi random sample of type 2 diabetic patients, and healthy subjects from their relatives.

Patients

During the study period, Dec. 2011, eighty eight type 2 diabetic patients, who visit the National Diabetes Center (NDC) / Al-Mustansiriyah University, had no coronary artery disease or hypertension (group1; mean age 49.0±10.7 years, ranged 30-73 years, male/female ratio = 1/0.76) and 70 of their healthy relatives participants (group2; mean age 46.5±8.5 years, ranged 32-63 years, male/female ratio = 1/0.84) were enrolled in the study. Our team designs the study to enroll only the type 2 diabetic patients who consulted NDC and fulfilled the WHO, IDF and NCEP/ATP III diagnostic criteria of type 2 diabetes mellitus [7,8,9].

All participants were thoroughly interviewed and examined by consultant physician according to the standard medical and laboratory work up which is adopted in the NDC; also they were examined physically and their heart rate, blood pressure, height, weight and BMI were measured.

Participant who had retinopathy, nephropathy was not included in the study. Cases with history of myocardial infarction, angina pectoris or other clinical findings of coronary artery diseases were not included in the study. Also, Cases who had right bundle-branch block, left bundle-branch block, Wolff-Parkinson-White syndrome, intraventricular conduction defect in resting ECG and angina chest pain or ischemic ECG changes during the exercise test were excluded from the study. Patients with a history of AF, having a permanent pacemaker, taking anti-arrhythmic medicine, having a thyroid disease, left ventricular hypertrophy, and/or left ventricular dysfunction were also excluded.

Electrocardiography and P-wave Measurements

The 12-lead surface electrocardiograms of all cases were obtained in a supine position with cardio smart, version 1.4, 22743582 GA(e), Germany, electrocardiography device. ECG was recorded at a paper speed of 50 mm/s and 1mV/cm standardization. When recording not allowed to hold their breath or speak. The ECG recordings were scanned with high resolution scanner (Canon, Cano scan, LED-25) flat bed scanner with resolution 600dpi. The onset of P-wave was defined as the junction between the isoelectric line and the start of P-wave deflection and the offset of the P-wave as the junction between the end of the P-wave deflection and the isoelectric line. Mean of P-wave duration in the 12 leads. Also P_{max} and P_{min} P-waves were calculated on a 12-lead surface ECG simultaneously recorded and their difference were defined as P-wave dispersion (Pd) ($Pd = P_{max} – P_{min}$).

Laboratory Analysis

Fasting blood sampels were taken from all patients during their visits for laboratory analysis to measure the fasting plasma glucose (FPG), glycated hemoglobin (HbA_{1c}), serum

cholesterol, serum triglycerides, HDL and LDL.

Statistical Analysis

The statistical analyses of the cases were done with SPSS software. All data were expressed as mean ± SD. Student's t-test was used in comparison of the means of the independent groups. A p-value <0.05 was considered as statistically significant in all analysis.

Simple linear correlation and regression analysis was used to study the type of relation between variables.

Results

The clinical characteristics of the cases in group 1 and group 2 are shown in (Table (1)). There was no significant statistical difference in comparison of groups with regard to age, sex, resting heart rate and body mass index, t-test, p>0.05.

Correlation and regression analysis of P-wave indices (mean P-wave duration P_{mean}, P_{max}, P_{min} and Pd) among group 1 participants shown absence of any correlation with the age, duration of diabetes, FPG, BMI, resting heart rate and HDL. But, correlation of P-wave indices among group 1 participants with HbA1c, Serum cholesterol, serum triglycerides and LDL were shown weak correlation.

All the details of P-wave indices of group 1 and group 2 were shown in (Table (2)). P_{mean}, P_{max} and Pd showed obvious higher values in diabetic patients; but, differences between group 1 and group 2 were statistically significant, t-test, P< 0.05. While, the difference between P_{min} values of group 1 and group 2 was not statistically significant.

Table (1)
Descriptive criteria of Group 1 and Group 2.

		Group 1 (n = 88) (diabetic participant)	*Group 2 (n = 70) (healthy relatives)*	*P value*
Age (years)[a]		49.0±10.7	46.5±8.5	NS
Sex	**Male n (%)**	50 (56%)	38 (54%)	NS
	Female n (%)	38 (44%)	32 (46%)	NS
Resting heart rate (pulse/min)		81.0±11.5	75.5±8.6	NS
BMI (kg/m^2)		30.0±5.5	26.57±3.61	<0.05
Duration of diabetes (year)		5.0±4.8	-----	
FPG (mmol/L)		9.879±3.296	4.784±0.788	<0.05
HbA1c (%)		9.0±1.9	5.5±0.82	<0.05
Serum cholesterol (mmol/L)		5.413±1.546	4.831±0.797	<0.05
Serum triglycerides (mmol/L)		1.966±0.991	2.403±0.221	<0.05
HDL (mmol/L)		1.346±0.559	1.554±0.404	NS
LDL (mmol/L)		3.185±1.147	3.232±1.181	NS

Table (2)
Comparison of P-Wave indices of study groups.

	Group 1 (n = 88) (diabetic participant)	*Group 2 (n = 70) (healthy relatives)*	*P value*
Mean P-wave (P_{mean}) (ms)	200.0±28.1	196.3±31.3	<0.05
Maximum P-wave (P_{max}) (ms)	300.0±49.1	285.7±28.6	<0.05
Minimum P-wave (P_{min}) (ms)	100.0±26.7	108.5±44.5	NS
P-wave dispersion (Pd) (ms)	200.0±51.5	177.1±44.2	<0.05

Discussion

Kose et al. 2003, did not observe differences in p-wave indices between genders of children [10], and Sari et al., 2008, reported similar findings in a small group of healthy males and females [11], also, Udi Nussinovitch, Jan. 2012, did not find association between gender and P-wave parameters [4]; but in contrast, Yildiz et al. 2008, included a very large cohort and reported that male gender was associated with higher Pd and P_{max} values [12]. Sari et al., Kose et al. and Udi Nussinovitch results were consistent with the findings in our study about relation of gender with P-wave indices [4, 11].

Study the relation of age with P-wave indices, as far as, the risk of AF increased dramatically in older patients [1, 13], and Kannel et.al found that prevalence of AF doubles with each advancing decade of age, from 0.5% at the age of 50-59 years to almost 9% at the age of 80-89 years [14]. We did not find any significant association between age and P-wave indices; also Yildiz et al. found no association between age and Pd [12]. But Magnani et al., in contrast, reported a positive association between age and all P-wave parameters [15].

Regarding the correlation between BMI and P-wave indices we did not find any correlation; but Udi Nussinovitch [4] found an interesting negative associations between increased BMI and Pd, moreover in a recently published review by Rosiak et al., 2010, it was reported that an increase of a single BMI unit was associated with an increase of about 8% in the risk for developing AF [16]. Also, higher Pd was reported in obese patients compared with patients with normal weight in studies specifically aimed at evaluating such an association [17, 18]. Another report by Magnani et al., 2010, found a negative association between BMI and Pd [15].

We found in our study that P-wave indices, P_{mean}, P_{max} and Pd of diabetic patients were higher than those of the healthy control group; and the difference of statistical significant. But the P_{min} did not show any significant difference between diabetic patients and healthy control group. Although, Mehmet et.al. [1] in 2007 stated that AF accompanies DM and increases the mortality, and they could not find any published study investigating Pd, which is one of the predictor of AF in diabetic cases; but, according to their knowledge, their study was the first one showing prolongation of Pd in diabetic cases without hypertension and ischemia. They did not refer to other in P-wave indices and since that study a lot of studies about the importance of p-wave were concentrated on the role and importance of Pd rather than the other P-wave indices which are the P_{mean} and P_{max} [1, 4, 10, 11, 12, 19].

It was shown that DM is an independent and strong risk factor for development of AF and Pd is the predictor of AF in diabetic cases [1, 20, 21]; the frequency of AF development was 1.4 - 2.1 folds higher in cases with DM than cases without DM [20]. Also, Pd is a non-invasive indicator of intra-atrial conduction heterogeneity producing substrate for re-entry, which is a pathophysiological mechanism of AF [1]. Moreover; Boriani et al reported that P-wave dispersion is the most important indicator of short-term recurrences of AF immediately after internal cardioversion, [22] Pd was also used as an indicator of AF development in cases of coronary bypass surgery performed [23]. In another study it was seen that Pd was significantly prolonged in cases with paroxysmal AF (PAF), in contrast to cases without paroxysmal AF [24]. All the conclusions and extrapolations extracted from the forwarded studies can be applied on the P-wave indices P_{mean}, P_{max} and Pd as far as the pathophysiological bases for the prolongation of P-wave indices were the same as explained by Mehmet et.al.; who speculated that the possible mechanism of the Pd prolongation in diabetic patients could be atrial myopathy and fibrosis due to chronic hyperglycemia and extracellular protein deposition which leads to heterogeneity in atrial conduction velocity [1].

P-wave indices were simple and non invasive technique for the prediction and follow up of AF and PAF in diabetic patients during management and follow up of diabetes.

Conclusions

The P-wave indices (P_{mean}, P_{max}, and Pd) were significantly higher in type 2 diabetic patients than values of healthy individuals. Gender, age and BMI have no significant

effects on P-wave indices. But, P-wave indices among diabetic patients have weak correlation with HbA1c, Serum cholesterol, serum triglycerides and LDL.

Study Limitations

The high variability of P-wave indices and overlapping of the results with those reported by inconsistent studies, might suggest that P-wave indices were limited sensitivity and specificity; and necessity for the standardization of P-wave indices to increase the reproducibility, sensitivity, and specificity of the study findings.

The most important limitations of study were that accuracy and reproducibility may significantly increase when PC-based on-screen measurements are applied. Studies may differ in applying manual versus automated measurements of digitalized ECG. Also, comparison of different studies, applying different measurement techniques, due to the lack of measurement standardization, is challenging for the comparison and standardization of research work about p-wave indices.

The P-wave indices vary due to technical, external influences such as seasonal effects and Internal influences such as anxiety, adequate sleep, effect of autonomic function and Diurnal variation.

Recommendations

Prolongation of P-wave indices could be used as a non-invasive indicator for prolonged atrial conduction that might develop in diabetic cases.

References

[1] Mehmet Yazici, Kurtulus Ozdemir, Bulent B Altunkeser, Mehmet Kayrak, M Akif Duzenli, M Akif Vatankulu, Ahmet Soylu, Mehmet S Ulgen. The effect of diabetes mellitus on the p-wave dispersion. Circ J.; 71(6): 880-3, Jun 2007.

[2] Andrzej Bissinger, Tomasz Grycewicz, Wlodzimierz Grabowicz, and Andrzej Lubinski. The effect of diabetic autonomic neuropathy on P-wave duration, dispersion and atrial fibrillation. Arch Med Sci.; 7(5): 806–812, October 2011.

[3] Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: The Framingham Study. N Engl J Med; 306: 1018– 1022, 1982.

[4] Udi Nussinovitch. Meta-Analysis of P-Wave Dispersion Values in Healthy Individuals: The Influence of Clinical Characteristics. Ann of Noninvasive Electrocardiol.; 17(1):28-35, 2012.

[5] Perzanowski C, Ho AT, Jacobson AK. Increased P-wave dispersion predicts recurrent atrial fibrillation after cardioversion. J Electrocardiol; 38: 43 – 46, 2005.

[6] Feridun Kosar M.D., Yüksel Aksoy M.D., Fahri Ari M.D., Lezzan Keskin M.D., Ibrahim Sahin M.D. P-Wave Duration and Dispersion in Obese Subjects. Ann of Noninvasive Electrocardiol.; 13:3-7, 2008.

[7] World Health Organization. Diabetes mellitus: Report of the WHO Study Group. World Health Organ Tech Rep Ser; 727:1-113, 1985.

[8] Diabetes facts, the prevalence of diabetes has reached epidemic proportions. International Diabetes Federation (IDF). Diabetes Atlas, 4th Edition. 2009.

[9] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); Final Report. National Cholesterol Education Program National Heart, Lung, and Blood Institute, National Institutes of Health NIH Publication No. 02-5215. pp 3163-3173, September 2002.

[10] Kose S, Kilic A, Iyisoy A, et al. P wave duration and P dispersion in healthy children. Turk J Pediatr; 45: 133–135, 2003.

[11] Sari I, Zengin S, Ozer O, et al. Chronic carbon monoxide exposure increases electrocardiographic P-wave and QT dispersion. Inhal Toxicol; 20:879-884, 2008.

[12] Yildiz M, Pazarli P, Semiz O, et al. Assessment of P-wave dispersion on 12-lead electrocardiography in students who exercise regularly. Pacing Clin Electrophysiol; 31:580-583, 2008.

[13] Michelena HI, Powell BD, Brady PA, et al. Gender in atrial fibrillation: Ten years later. Gend Med; 7:206-217, 2010.
[14] Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol.; 82:2N–9N, 1998.
[15] Magnani JW, Johnson VM, Sullivan LM, et al. P-wave indices: Derivation of reference values from the Framingham Heart Study. Ann Noninvasive Electrocardiol; 15:344- 352, 2010.
[16] Rosiak M, Dziuba M, ChudzikM, et al. Risk factors for atrial fibrillation: Not always severe heart disease, not always so 'lonely.' Cardiol J; 17:437–442, 2010.
[17] Seyfeli E, Duru M, Kuvandik G, et al. Effect of obesity on P-wave dispersion and QT dispersion in women. Int J Obes (Lond); 30:957–961, 2006.
[18] Kosar F, Aksoy Y, Ari F, et al. P-wave duration and dispersion in obese subjects. Ann Noninvasive Electrocardiol; 13:3–7, 2008.
[19] Anonymous. Preliminary report of stroke prevention in atrial fibrillation study. N Engl J Med; 322: 863 – 868, 1990.
[20] Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. Int J Cardiol; 105: 315 – 318, 2005.
[21] Ostgren CJ, Merlo J, Rastam L, Lindblad U. Atrial fibrillation and its association with type 2 diabetes and hypertension in Swedish community. Diabetes Obes Metab; 6: 367 – 374, 2004.
[22] Boriani G, Diemberger I, Biffi M, Camanini C, Valzania C, Corazza I, et al. P wave dispersion and short-term vs late atrial fibrillation recurrences after cardioversion. Int J Cardiol; 101: 355 – 361, 2005.
[23] Tukek T, Akkaya V, Atilgen D, Demirel E, Ozcan M, Guven O, et al. Effect of left atrial size and function on P-wave dispersion: A study in patients with paroxysmal atrial fibrillation. Clin Cardiol; 24: 676–680, 2001.
[24] Weber UK, Osswald S, Huber M, Buser P, Skarvan K, Stulz P, et al. Selective versus nonselective antiarrhythmic approach for prevention of atrial fibrillation after coronary surgery: Is there a need for preoperative risk stratification?: A prospective placebo-controlled study using low-dose sotalol. Eur Heart J; 19:794– 800, 1998.

الخلاصة

خلفية البحث: لداء السكّري تأثير سلبي على القلب؛ إعتبرتْ معايير موجة **P** لغرض التعرف على التقطعِ والتوليدِغير المتجانس لأندفاع الجيبِ الأذيني وإطالةِ وقتِ التوصيلِ الأُذيني.

أهداف البحث: لمعْرِفة أهميةِ معايير موجة **P** واهمية إستعمالِها للتنبؤِ وتقييمِ مضاعفات السُكّريِ نوعِ ٢ للمصابين بالسُكري.

طرق البحث والنَتائِج: اجريت الدراسة في ديسمبر/كانون الأول ٢٠١١، على المصابون بالسُكرِي **(n =88)** وأقرباءهم الأصحاء **(n = 70)** تمت الدراسة في المركز الوطني للسكري. اثبتت الدراسة عند مقارنة كلتا المجموعتين بالنسبة للعُمرِ، الجنس، معدّل نبضات القلب في الأستراحة ومعيار كتلة الجسم عدم وجود اختلافات ذات (قيمة**P** اقل من ٠.٠٥). أظهرت معايير موجة **P** للمصابين بالسُكري غيابَ أيّ إرتباط بالعُمرِ، مدّة مرض السكّرِ، سكر الدم الصائم ، معيار كتلة الجسم ، معدّل نبضات القلب في الأستراحة و **HDL**؛ لكنها، اظهرت إرتباطاً ضعيفاً مَع**HbA1c** ، مستوى الكولستيرول بالمصل، مستوى الدهون الثلاثية و**LDL**. أظهرت معايير موجة **P** قِيَمَاً أعلى بدلالة احصائية لدى المصابون بالسُكرِي مِما لدى الأشخاص الأصحاء (قيمة**P** اقل من٠.٠٥، ماعداP_{min} (قيمة**P** اكثر من٠.٠٥)..

الإستنتاجات: معايير موجةP (P_{mean}، P_{max}، وPd) كَانتْ أعلى عند المصابون بالسُكرِي مِنْ الأفرادِ الأصحّاء. معايير موجة P عند المصابون بالسُكريِ لَيْسَ لَها تأثرُ بالجِنسِ، العُمر ومعيار كتلة الجسم؛ لكن، لَهُ إرتباطُ ضعيفُ مَع HbA1c، مستوى الكولوستيرول في المصلِ، مستوى الدهون الثلاثية و LDL .