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New electrocardiographic parameters and risk of atrial arrhythmias in INOCA patients

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ABSTRACT

Aims: Ischemia with no obstructive arteries (INOCA) is a clinical condition in which symptoms and signs of coronary artery disease are present, but coronary angiography does not show severe vessel narrowing. Atrial fibrillation (AF) is a common arrhythmia in cardiology practice, with an increasing prevalence with age and concomitant heart disease. P-wave dispersion (PWD) is an electrocardiographic (ECG) parameter defined as the difference between the maximum and minimum P-wave duration. There is an increasing number of studies showing an association between PWD and cardiovascular events. In this study, we aimed to evaluate the risk of AF in INOCA patients by detecting PWD, a new ECG parameter.

Methods: The study included 51 INOCA patients and 36 healthy subjects as a control group. The groups were compared in terms of demographic characteristics, laboratory findings, echocardiography, and ECG findings. The difference between the longest P wave (Pmax) and the shortest P wave (Pmin) was considered as PWD (PWD=Pmax-Pmin).

Results: When the patient group was compared with the control group, no difference was detected in terms of demographic characteristics or laboratory findings. When compared with the control group, Pmax duration and Pd values were significantly longer in the patient group compared to the control group (Pmax durations 112.7±7.09 ms and 98.1±5.5 ms, respectively, $p<0.001$; Pd durations 43.0±9.4 ms and 31.4±12.4 ms, respectively, $p<0.001$). On the other hand, Pmin durations did not differ significantly between the groups ($p>0.05$).

Conclusion: We observed that PWD was higher in INOCA patients compared to controls, and our results suggest that INOCA patients are at risk for AF.

Keywords: Ischemia with no obstructive arteries, P-wave dispersion, atrial fibrillation

INTRODUCTION

Ischemia with no obstructive arteries (INOCA) is a clinical condition with clinically stable symptoms and signs of ischemic heart disease despite normal or near-normal coronary arteries in angiography. The incidence of this syndrome, which was included in the Cardiology Guidelines for the first time in 2021, has been reported to be between 50-65% in women and 17-32% in men.[1-3] Approximately 30% of patients with coronary artery disease (CAD) have concomitant atrial fibrillation (AF).[4] AF independently increases the risk of death by 39% in patients with stable CAD. Patients with stable CAD and concomitant AF have almost twice the risk of stroke compared with patients with stable CAD without AF.[5]

AF, which is the most common rhythm disorder in clinical practice, is of critical importance because of the hemodynamic disturbances and thromboembolic events it brings with it.[6] Although the mechanisms causing AF are not fully understood, many risk factors, including age, hypertension (HT), CAD, cerebrovascular disease, and diabetes mellitus (DM), are thought to play a role in the development of AF.[7] Moreover, accumulating evidence has shown that myocardial damage and ischemia, inflammation and inflammatory factors, the autonomic nervous system, and oxidative stress play an important role in the pathogenesis of AF.[8-11]

P-wave dispersion (PWD), defined as the difference between the maximum and minimum P-wave duration on surface electrocardiography (ECG), is a new ECG marker associated with the inhomogeneous and discontinuous propagation of sinus impulses.[12] The correlation between the presence of inter- and intra-atrial conduction abnormalities and the induction of paroxysmal AF (PAF) is well documented.[13] Estimating the likelihood of patients developing PAF can guide the clinician in the management and stratification of patients at a higher risk of developing AF.

To our knowledge, cardiac evaluation using PWD has not been previously performed in INOCA patients. Therefore, we aimed to investigate whether AF can be predicted by evaluating PWD in these patients.

METHODS

The study was carried out with the permission of Ethical Committe of Faculty of Medicine of Erciyes University (Date:16.12.2020, Decision No: 2020-35). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients aged 18-85 years who presented to the Erciyes University Faculty of Medicine outpatient clinic with chest pain and/or exertional dyspnea due to ischemia, underwent coronary angiography, and did not have obstructive epicardial CAD on coronary angiography (coronary artery stenosis ratio ≥50% and/or fractional flow reserve <0.8) were included in the study. The study was conducted between November 2019 and November 2023 and included 51 INOCA patients. Thirty-six demographically similar patients without ischemic chest pain who underwent a stress test for any reason and had a negative stress test were considered the control group.

All patients underwent a detailed history, physical examination, 12-lead ECG, complete blood count, and serum biochemistry tests. A detailed transthoracic echocardiographic (ECHO) examination was performed in all patients. No atrial or ventricular conduction abnormality was detected on ECGs in the patient group or the control group. In addition, none of the patients included in the study had a history of PAF. Patients with a history of ischemic heart disease, patients without sinus rhythm and with pacemakers, patients with segmental or global wall motion abnormalities, patients with moderate to severe valvular heart disease, and patients with structural heart disease, endocrine neoplasms, parathyroid cancer, patients with thyroid cancer or hyperparathyroidism, renal failure, hypertrophic cardiomyopathy, hypokalemia and hyperkalemia, hypomagnesemia and hypermagnesemia, creatinine clearance (CrCl) <60 ml/min, body mass index (BMI) <30 kg/m^2, and severe comorbidities were excluded.

Electrocardiogram Analysis

All standard 12-lead ECGs were obtained in the supine position and at rest using an ECG device (Philips brand) standardized to 1 mV/cm and 25 mm/s paper speed. All ECGs were scanned and transferred to personal computers. ECGs were magnified 5-fold and measured using an electronic caliper (Cardio Calipers software version 3.3; Iconico.com, Philadelphia, PA, USA) for the necessary measurements.

The starting point of the P wave was considered the intersection of the isoelectric line and the P wave, and the endpoint of the P wave was considered the intersection of the isoelectric line and the terminal point of the P wave. The maximum P wave (Pmax) duration was considered to be the longest atrial conduction time. The difference between the longest P wave (Pmax) and the shortest P wave (Pmin) was considered PWD (PWD=Pmax-Pmin). All calculations were evaluated by two cardiologists who were blinded to the clinical characteristics of the patients.

Echocardiography

Patients and healthy volunteers underwent conventional ECHO imaging with an M4S-RS (1.5-3.6 MHz) cardiac transducer and Vingmed System 7 (General Electronic Horten, Norway) ECHO. Left ventricular diastolic (LVIDd) and systolic (LVIDs) diameters, interventricular septum (IVSWT), and posterior wall (LVPWT) diastolic thicknesses were measured in the parasternal long axis with M-mode ECHO according to the standards defined by the American Medical Association. The ejection fraction on ECHO was calculated using the Teichholz formula.[14]

Statistical Analysis

Statistical analyses were performed using SPSS Statistics software package version 21.0 (SPSS Inc., Chicago, IL, USA) for Windows. The distribution characteristics of the data were determined by using the Kolmogorov-Smirnov test. Independent samples A t-test was used for parametric scale variables. Mann-Whitney the U test was used for nonparametric scale variables. The $\chi 2$ (chi-squared) test was used for univariate analysis of the categorical variables. The variables were reported as means ± SD (standard deviation), whereas the categorical variables were reported as percentages. Correlation analyses were performed using Pearson and Spearman coefficients of correlation. A probability value of $p < 0.05$ was considered to be significant, and two-tailed p values were used for all statistical analyses.

RESULTS

The baseline characteristics of the patient and control groups are given in **Table 1**. There was no statistically significant difference between the two groups in terms of demographic and clinical parameters, such as age, gender, presence of HT, presence of DM, smoking status, and baseline blood parameters ($p>0.05$). The ECHO parameters of the patient and control groups are shown in **Table 1**. There was no statistically significant difference between the two groups in terms of the ECHO parameters. Heart rate and PR intervals were similar in both groups.

Table 1. Baseline clinical, demographic and echocardiographic features of the study groups

Variables	Control Group (n=36)	INOCA Group	p value
Age (years)	52.7±11.2	51.4±7.4	0.742
Male/female	25/11	37/14	0.655
HT	7 (%19.4)	11 (%21.6)	0.439
DM	3 (%8.3)	6 (%11.8)	0.772
Smoke	4 (%11.7)	7 (%16.2)	0.645
Systolic blood pressure, mm Hg	119.4±15.2	121.3±10.9	0.712
Diastolic blood pressure, mm Hg	71.28±10.3	69.9±9.7	0.385
Glucose (mg/dL)	89.4±9.3	92.1±11.3	0.225
Creatinine (mg/dL	1.0±2.1	0.9±1.9	0.298
Total cholesterol	185.7±33.2	191.1±42.4	0.743
HDL	42.9±11.5	39.5±9.4	0.199
LDL	116.2±31.5	121.65±48.7	0.941
TG	165.7±70.6	155.4±66.9	0.445
AST (U/L)	23.6±8.4	20.9±6.9	0.813
ALT (U/L)	21.4±8.1	23.0±8.3	0.221
WBC (10^3/uL)	8.3±2.1	7.55±2.5	0.673
Hemoglobin (g/l)	13.1±0.9	15.2±1.9	0.334
Platelet (/mm3)	280.8±61.5	253.5±81.5	0.568
LVEF	65.1±4.7	58.6±2.9	0.378
LVEDD (cm)	4.1±0.8	4.4±2.2	0.509
LVESD (cm)	3.4±0.5	3.55±2.3	0.692
IVSD (cm)	0.9±0.4	1.0±0.3	0.436
PWD (cm)	.9±0.7	1.1±0.3	0.591

Data are expressed as mean ± standard deviation for normally distributed data and percentage (%) for categorical variables. DM: Diabetes Mellitus, HT: Hypertension, HDL; High density lipoprotein, LDL; low density lipoprotein, TG; Triglyceride, WBC: White Blood Cell. LVEDD: Left Ventricular End Diastole Diameter, LVESD: Left Ventricular End Systole Diameter, IVSD: Interventricular Septal Diameter, PWD: Posterior Wall Diameter, LVEF; Left Ventricular Ejection Fraction

Pmax duration and Pd values of the patient group were significantly longer than those of the control group (Pmax durations 112.7±7.09 ms and 98.1±5.5 ms, respectively, p<0.001; Pd durations 43.0±9.4 ms and 31.4±12.4 ms, respectively, p<0.001; **Table 2**). On the other hand, Pmin times did not differ significantly between the groups (p>0.05).

Table 2. Electrocardiographic Characteristics of the study population

Variables	Control Group (N=36)	INOCA Group	p value
Heart rate (min)	82.7±11.2	86.25±3.2	0.109
PR interval (ms)	144 ± 9	142 ± 5	0.798
P Max(ms)	98.1±5.5	112.7±8.9	**p<0.001**
P Min (ms)	66.2±8.1	68.1±6.6	0.235
PD (ms)	31.4±12.4	43.0±9.4	**p<0.001**

Pmax = maximum P-wave duration; Pmin = minimum P-wave duration; Pd = P-wave dispersion, Min = Minute, ms = millisecond

DISCUSSION

In this study, PWD on a 12-lead superficial ECG was found to be significantly higher in INOCA patients. To the best of our knowledge, this is the first study in the literature.

In INOCA, the risk of developing myocardial infarction, cardiovascular death, stroke, and heart failure may increase up to 10-fold compared to the normal population.[15,16] If accompanied by DM and HT, the mortality rate increases even more.[15] Some studies have claimed that patients with INOCA have a worse quality of life, more limited physical activity, and a higher frequency of angina compared to patients with stable CAD.[16] These patients require more frequent hospitalization and more frequent angiography.

PWD is a new ECG marker associated with the heterogeneous and discontinuous propagation of sinus impulses. Moreover, the association between the presence of intra-atrial conduction abnormalities and the induction of PAF is well documented.[17-19] PWD has also been found to be associated with carotid atherosclerosis.[20] PWD has also been shown to increase the coronary slow flow phenomenon.[21] PWD has been reported to be significantly associated with left ventricular diastolic dysfunction.[22] Tukek et al.[23] showed that a shorter minimum P wave duration was associated with PAF in patients with an increased left atrial diameter. Dilaveris et al.[24] reported that shorter P-wave duration was an independent predictor of extensive AF. Haşimi et al.[25] showed that a shorter minimum P-wave duration was an important determinant of AF in patients undergoing coronary artery bypass surgery. Altun et al.[26] showed that PWD was longer in patients with Syndrome X compared to the normal population. Ariyarajah et al.[27] showed a significant relationship between increased P-wave duration (prolonged atrial depolarization) and AF recurrence in myocardial infarction patients without ST elevation. In our study, we found an increase in PWD. This increase in PWD may be a determinant of the possible development of AF in INOCA.

The pathophysiology of AF development in INOCA patients may be quite complex. However, the following mechanisms can be speculated as the causes: first, the atrial blood supply is reduced in the coronary arteries, even at the microvascular level, and atrial reentry mechanisms are accelerated.[28,29] Second, atrial pressure increases as a result of atrial ischemia and causes atrial changes (compression ischemia) due to stretching of the atrial walls, leading to natriuretic peptide release.[30-34] Third, inflammation occurs in the atrium with ischemia and plays an important role in the development of AF with increased inflammatory response and oxidative stress.[35-39] Another one suggests that increased sympathetic activity in CAD leads to heterogeneous changes in atrial refractoriness, causing reentrant waves and having an effect on the development of AF.[40,41]

CONCLUSION

Although our study was not a follow-up study, we observed that PWD, a technique to predict cardiac arrhythmias, was significantly longer in INOCA patients. Our results suggest that INOCA patients are at risk for AF. Identifying individuals with INOCA who are at higher risk of developing AF may facilitate early detection of AF. Therefore, we believe that the results of this study are clinically relevant.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ethical Committe of Faculty of Medicine of Erciyes University (Date:16.12.2020, Decision No: 2020-35). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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REFERENCES

1. Gulati M, Levy PD, Mukherjee D, et al. AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: executive summary: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation*. 2021;144(22):e368-454.
2. Hansen B, Holtzman JN, Juszczynski C, et al. Ischemia with No Obstructive Arteries (INOCA): A Review of the Prevalence, Diagnosis and Management. *Curr Probl Cardiol*. 2023;48(1):101420.
3. Bastiany A, Pacheco C, Sedlak T, et al. A practical approach to invasive testing in ischemia with no obstructive coronary arteries (INOCA). *CJC Open*. 2022;4(8):709-720.
4. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet (London, England)*. 2014;383:955-962.
5. Saglietto A, Varbella V, Ballatore A, Xhakupi H, Ferrari GM, Anselmino M. Prognostic implications of atrial fibrillation in patients with stable coronary artery disease: a systematic review and meta-analysis of adjusted observational studies. *Rev Cardiovasc Med*. 2021;22(2):439-444.
6. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21):e1-e76.
7. Miller JD, Aronis KN, Chrispin J, et al. Obesity, exercise, obstructive sleep apnea, and modifiable atherosclerotic cardiovascular disease risk factors in atrial fibrillation. *J Am Coll Cardiol*. 2015;66(25):2899-2906.
8. Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? *Eur Heart J*. 2006;27:136-149.

9. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. *J Am Coll Cardiol.* 2007;50(21):2021-2028.
10. Ozaydin M, Peker O, Erdogan D, et al. Oxidative status, inflammation, and postoperative atrial fibrillation with metoprolol vs carvedilol or carvedilol plus N-acetyl cysteine treatment. *Clin Cardiol.* 2014;37(5):300-306.
11. Thompson AE, Hirsch GM, Pearson GJ. Assessment of new onset postcoronary artery bypass surgery atrial fibrillation: current practice pattern review and the development of treatment guidelines. *J Clin Pharm Ther.* 2002;27(1):21-37.
12. Magnani JW, Mazzini MJ, Sullivan LM, Williamson M, Ellinor PT, Benjamin EJ. P-wave indices, distribution and quality control assessment (from the Framingham Heart Study). *Ann Noninvasive Electrocardiol.* 2010;15(1):77-84.
13. Liu Z, Hayano M, Hirata T, et al. [Abnormalities of electrocardiographic P wave morphology and the relationship to electrophysiological parameters of the atrium in patients with idiopathic paroxysmal atrial fibrillation]. *J Cardiol.* 1998;32(3):189-196.
14. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;16(3):233-271.
15. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med.* 2009;169 (9):843-850.
16. Schumann CL, Mathew RC, Dean JL, et al. Functional and economic impact of INOCA and influence of coronary microvascular dysfunction. *JACC Cardiovasc Imaging* 2021;14(7):1369-1379.
17. Dilaveris PE, Gialafos EJ, Sideris SK, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. *Am Heart J.* 1998;135(5):733-738.
18. Dilaveris PE, Gialafos EJ, Andrikopoulos GK, et al. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. *Pacing Clin Electrophysiol.* 2000;23(3):352-358.
19. Aytemir K, Ozer N, Atalar E, et al. P wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol.* 2000;23(7):1109-1112.
20. Ozuğuz U, Ergün G, Işık S, et al. Association between C-reactive protein, carotid intimamedia thickness and P-wave dispersion in obese premenopausal women: an observational study. *Anadolu Kardiyol Derg.* 2012;12(1):40-46.
21. Turkmen M, Barutcu I, Esen AM, Karakaya O, Esen O, Basaran Y. Effect of slow coronary flow on P-wave duration and dispersion. Angiology 2007;58(4):408-412.
22. Gunduz H, Binak E, Arinc H, et al. The relationship between P wave dispersion and diastolic dysfunction. *Tex Heart Inst J.* 2005;32(2):163-167.
23. Tukek T, Akkaya V, Atilgan D, et al. Effect of left atrial size and function on P-wave dispersion:A study in patients with paroxysmal atrial fibrillation. *Clin Cardiol.* 2001;24(10):676-680.
24. Dilaveris PE, Gialafos EJ, Chrissos D, et al. Detection of hypertensive patients at risk for paroxysmal atrial fibrillation during sinus rhythm by computer assisted P wave analysis. *J Hypertens.* 1999;17(10):1463-1470.
25. Hashemi Jazi M, Amirpour A, Zavvar R, Behjati M, Gharipour M: Predictive value of P wave duration and dispersion in post Coronary artery bypass surgery atrial fibrillation. *ARYA Atherosclerosis.* 2012; 8(2):59-62.
26. Altun A, Erdogan O, Tatli E, Ugur-Altun B, Durmus-Altun G, Ozbay G. Increased P wave dispersion: a new finding in patients with syndrome X. *Can J Cardiol.* 2002;18(11):1207-1210.
27. Ariyarajah V, Malinski M, Khadem A, Harizi R, Wolfe K, Spodick DH. Relation of recurrence of atrial fibrillation after nonST-elevation acute myocardial infarction to left atrial abnormality. *Am J Cardiol.* 2008;101(1):30-34.
28. Eggers KM, Hjort M, Baron T, et al. Morbidity and cause-specific mortality in first-time myocardial infarction with nonobstructive coronary arteries. *J Intern Med.* 2019;285(4):419-428.
29. Gorenek B, Kudaiberdieva G. Atrial fibrillation in acute ST-elevation myocardial infarction: clinical and prognostic features. *Curr Cardiol Rev.* 2012;8(4):281-289.
30. El-Shetry M, Mahfouz R, Frere AF, Abdeldayem M. The interplay between atrial fibrillation and acute myocardial infarction. *Br J Hosp Med (Lond).* 2021;82(2):1-9.
31. Jons C, Joergensen RM, Hassager C, et al. Diastolic dysfunction predicts new-onset atrial fibrillation and cardiovascular events in patients with acute myocardial infarction and depressed left ventricular systolic function: a CARISMA substudy. *Eur J Echocardiogr.* 2010;11(7):602-607.
32. Aronson D, Mutlak D, Bahouth F, et al. Restrictive left ventricular filling pattern and risk of new-onset atrial fibrillation after acute myocardial infarction. *Am J Cardiol.* 2011;107(12):1738-1743.
33. Yilmaz R, Kasap H, Baykan M, et al. Assessment of left ventricular function by Doppler tissue imaging in patients with atrial fibrillation following acute myocardial infarction. *Int J Cardiol.* 2005;102(1):79-85.
34. Rodrigues AB, Gismondi RA, Lagoeiro A, et al. Association between B-type natriuretic peptide and within-visit blood pressure variability. *Clin Cardiol.* 2018;41(6):778-781.
35. Hwang HJ, Ha JW, Joung B, et al. Relation of inflammation and left atrial remodeling in atrial fibrillation occurring in early phase of acute myocardial infarction. *Int J Cardiol.* 2011;146(1):28-31.
36. Aronson D, Boulos M, Suleiman A, et al. Relation of C-reactive protein and new-onset atrial fibrillation in patients with acute myocardial infarction. *Am J Cardiol* 2007;100(5):753-757.
37. Yilmaz Y, Kelesoglu S, Elcik D, Ozmen R, Kalay N. Predictive values of systemic immune-inflammation index in new-onset atrial fibrillation following coronary artery bypass grafting. *Braz J Cardiovasc Surg.* 2023;38(1):96-103.
38. Ulus T, Isgandarov K, Yilmaz AS, Vasi I, Moghanchızadeh SH, Mutlu F. Predictors of new-onset atrial fibrillation in elderly patients with acute coronary syndrome undergoing percutaneous coronary intervention. *Aging Clin Exp Res.* 2018;30(12):1475-1482.
39. Liu L, Gan S, Li B, Ge X, Yu H, Zhou H. Fisetin Alleviates Atrial Inflammation, Remodeling, and Vulnerability to Atrial Fibrillation after Myocardial Infarction. *Int Heart J.* 2019;60(6):1398-1406.
40. Chang CM, Wu TJ, Zhou S, et al. Nerve sprouting and sympathetic hyperinnervation in a canine model of atrial fibrillation produced by prolonged right atrial pacing. *Circulation.* 2001;103(1):22-25.
41. Jayachandran JV, Sih HJ, Winkle W, Zipes DP, Hutchins GD, Olgin JE. Atrial fibrillation produced by prolonged rapid atrial pacing is associated with heterogeneous changes in atrial sympathetic innervation. *Circulation.* 2000;101(10):1185-1191.