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Electrocardiographic P-wave peak time predicts significant ischemia in INOCA patients: A pilot study

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ABSTRACT

Background: Ischemia with non-obstructive coronary arteries (INOCA) represents a diagnostic and therapeutic challenge, often related to coronary microvascular dysfunction (CMD). Identifying non-invasive electrocardiographic markers that predict ischemia in this population remains a clinical priority. P-wave peak time (PWPT), reflecting atrial conduction delay, has been linked to ischemic pathophysiology.

Methods: This retrospective, observational study included 444 patients who underwent coronary angiography with normal epicardial arteries followed by SPECT myocardial perfusion imaging (MPI) due to persistent anginal symptoms. Patients were classified into three groups based on the percentage of reversible left ventricular ischemia: <5 %, 5–10 %, and > 10 %. P-wave indices—including PWPT in leads DII and V1—were measured digitally by two independent observers. Multivariate logistic regression identified independent predictors of >10 % ischemia. ROC analysis assessed the discriminative power of PWPT.

Results: PWPT-DII and PWPT-V1 were significantly prolonged in patients with >10 % ischemia (63 ± 8 ms and 58 ± 9 ms, respectively) compared to patients with <5 % ischemia (55 ± 7 ms and 50 ± 8 ms; both $p < 0.001$). PWPT-DII yielded an AUC of 0.82 (95 % CI 0.77–0.86), outperforming PWPT-V1 (AUC 0.76). In multivariate models, PWPT-DII (OR 1.15, 95 % CI 1.08–1.23), PWPT-V1 (OR 1.10, 95 % CI 1.03–1.17), age, diabetes mellitus, and E/e' ratio emerged as independent predictors of significant ischemia.

Conclusions: Prolonged PWPT, particularly in lead DII, was observed to be independently associated with myocardial ischemia in INOCA. Incorporating PWPT into standard ECG interpretation may aid in risk stratification and early identification of CMD in patients with normal coronary angiograms but ongoing ischemic symptoms.

Introduction

Ischemia with Non-Obstructive Coronary Arteries (INOCA) describes patients who present with anginal symptoms and objective evidence of myocardial ischemia, yet exhibit no angiographically-proven obstructive coronary artery disease (stenosis <50 %) [1]. Although previously considered benign, mounting evidence demonstrates that INOCA remains a genuine and underrecognized clinical entity despite its increasing prevalence and adverse prognostic implications [2].

The prevalence of INOCA is substantial, affecting nearly 60 % of women and 30 % of men undergoing angiography for stable angina [1]. According to a meta-analysis of 54 studies, INOCA may affect 13 % of patients with moderate-to-severe ischemia revealed by imaging [2]. Large-scale analyses have linked INOCA to increased risks of hospitalization for heart failure, major adverse cardiovascular events, and a reduction in quality of life [3].

INOCA includes two primary mechanisms: coronary microvascular dysfunction (CMD) and epicardial vasospasm, which may coexist [4]. CMD, which results from structural and/or functional alterations in the coronary microcirculation, has been documented in up to 75 % of INOCA patients using non-invasive or invasive methods [4]. Although diagnostic gold standards like coronary flow reserve (CFR) and microvascular resistance require invasive or advanced imaging methods, myocardial perfusion imaging (MPI) via single photon emission computed tomography (SPECT) proves practical as well as validated alternative in the assessment of ischemia in INOCA [5].

Despite the increasing emphasis on INOCA, the electrocardiographic manifestations of microvascular ischemia remain underexplored.

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Growing interest in early, noninvasive markers of atrial conduction delay, such as P-wave indices, suggests their potential utility in identifying subtle myocardial disturbances. These parameters, including P-wave duration (PWdur), dispersion (PWd), terminal force (PWTFV1), and peak times (PWPT), offer insight into atrial electrophysiological remodeling that may parallel microvascular perfusion abnormalities [6]. Previous studies have demonstrated that P-wave indices on standard 12-lead ECG correlate with microvascular and diastolic abnormalities in cases possessing ischemic heart disease. For instance, PWPT has been shown to be prolonged in individuals with the coronary slow-flow phenomenon, reflecting impaired microvascular perfusion and associated diastolic dysfunction [7]. Similarly, another study showed that preprocedural PWPT in lead DII independently predicted no-reflow during the angiography following percutaneous coronary intervention, highlighting PWPT's role as a marker of microvascular reperfusion success [8].

Despite these insights in acute and slow-flow ischemic syndromes, the relationship between P-wave indices and myocardial ischemia in INOCA, a clinical entity that remains underrecognized despite its increasing prevalence and prognostic relevance, has not been systematically examined. Given that INOCA encompasses patients with ischemic symptoms and objective perfusion defects despite angiographically normal epicardial arteries, we hypothesized that PWdur, PWd, PWTFV1, and PWPT would similarly reflect the burden of microvascular ischemia in these patient populations. Therefore, the present study was designated to determine if these ECG-derived parameters are associated with the extent of reversible ischemia on SPECT MPI in INOCA, potentially providing a simple, noninvasive tool for risk stratification and early detection of microvascular dysfunction.

Methods

This observational and cross-sectional study retrospectively evaluated patients undergoing coronary angiography in our cardiology department due to angina-like chest pain between January 2020–December 2024. Electronic health records were screened to identify individuals with angiographically normal epicardial coronary arteries. Among 7500 patients evaluated, 2550 had angiographically normal epicardial coronary arteries. Of these, 596 were referred for SPECT-MPI due to persistent symptoms. Following the exclusion of 152 patients according to established clinical and technical criteria, a total of 444 patients with comprehensive ECG, echocardiographic, and perfusion imaging data were retained for the ultimate analysis. Patient inclusion process was illustrated in Fig. 1.

Patients possessing any condition that could interfere with atrial conduction or affect the accuracy of P-wave indices were excluded from the study. Specifically, a history of atrial fibrillation or flutter, pacemaker implantation or paced rhythm, structural heart disease (including cardiomyopathies, congenital heart defects, or moderate to severe left ventricular hypertrophy), moderate to severe valvular heart disease, and left or right bundle branch block on electrocardiogram comprised our exclusion criteria. Additional exclusions included advanced chronic kidney disease (eGFR <30 mL/min/1.73 m^2), hepatic failure, known thyroid dysfunction (either hyperthyroidism or hypothyroidism), electrolyte imbalance (e.g., hypo- or hyperkalemia, hypomagnesemia), and incomplete ECG, echocardiographic, or SPECT MPI data in the hospital archives.

The research protocol received approval from the Institutional Ethics Committee of Kirsehir Ahi Evran University. The study was performed in compliance with the ethical standards set forth in the Declaration of Helsinki. As the study design was retrospective, obtaining informed consent from participants was not required.

Electrocardiographic acquisition and p-wave measurements

Standard resting 12-lead ECG recordings were obtained while patients were lying in the supine position after a minimum rest period of 10 min. The ECGs were recorded at a paper speed of 25 mm/s with a calibration of 10 mm/mV. Each tracing was exported as a high-resolution (600 dpi) digital file and subsequently imported into Adobe

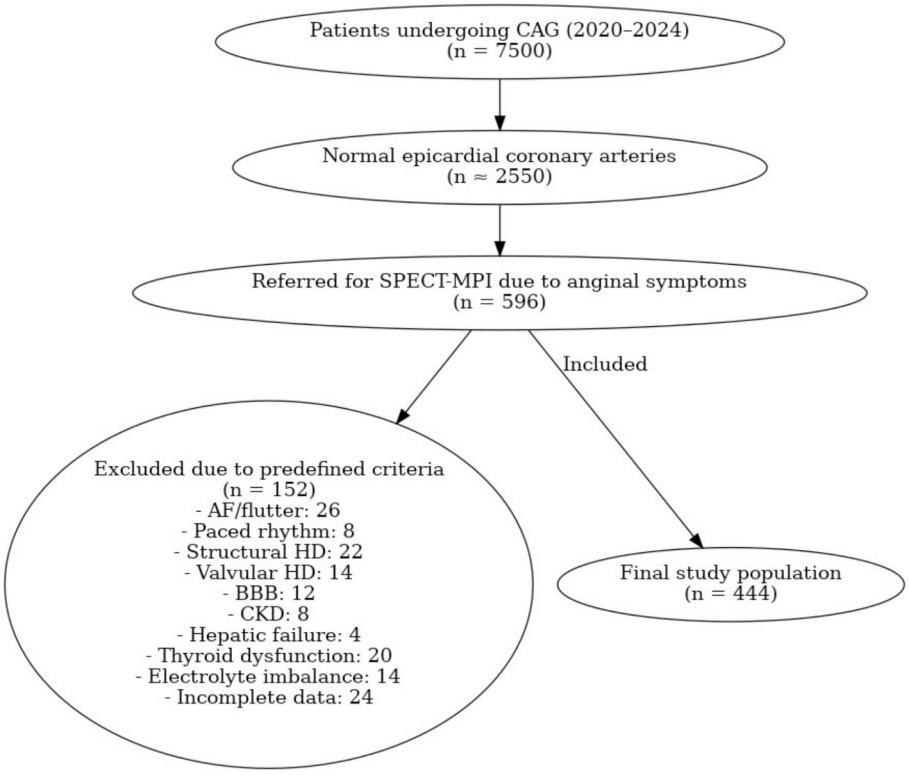

Fig. 1. Patient inclusion flowchart.

Photoshop software to enable accurate electronic measurements. Images were magnified for detailed evaluation, and measurements were performed using the digital caliper tool.

Two experienced cardiologists, blinded to the clinical and imaging data, independently conducted all measurements. P-wave onset was defined as the place where the waveform first deviated from the isoelectric line, and the offset as the point where it returned. PWdur was measured in lead DII, and PWd was defined as the interval calculated by subtracting the shortest P-wave duration from the longest one among all evaluable leads. P-wave peak time (PWPT) was measured from the onset of the P-wave to the point of maximum positive amplitude in leads DII and V1, or to the nadir of negative deflection in V1 if it is negative or biphasic [8,9]. The P-wave terminal force in lead V1 (PWTFV1) was calculated by multiplying the amplitude (in mm) by the duration (in ms) of the terminal negative portion of the P-wave in that lead.

Heart rate, QT, QTc, and T peak-to-end (TPE) intervals were all performed using lead II, which provides optimal visualization of the QRS complex and T wave. Heart rate was calculated by measuring the RR interval and applying the formula: Heart rate = 1500 / RR interval (in millimeters). The QT interval was defined as the time from the onset of the QRS complex to the end of the T wave. To account for heart rate variability, the corrected QT interval (QTc) was calculated using Bazett's formula: $QTc = QT / \sqrt{RR}$. Additionally, TPE interval was measured as the interval from the peak of the T wave to its end. Reproducibility of the measurements was evaluated by calculating intraobserver and interobserver coefficient of variation (CV) values. The intraobserver CV was 3.8 %, and the interobserver CV was 4.5 %, indicating high measurement consistency.

Echocardiography

Echocardiographic evaluations for all subjects were performed using a Vivid S5 device (GE Vingmed, Horten, Norway). Two-dimensional and M-mode images were obtained from standard parasternal long- and short-axis views and apical two- and four-chamber windows. Biplane Simpson's technique using apical views were implemented to measure the left ventricular ejection fraction (LVEF). At end-systole, the left atrial (LA) area was traced in the apical four-chamber view, excluding pulmonary veins and the LA appendage, and the mean value of three beats was recorded. Diastolic function assessment included pulsed-wave Doppler analysis of transmitral inflow (peak E and A velocities, E/A ratio, and deceleration time) and tissue Doppler imaging (TDI) of the mitral annulus. Early diastolic (e') velocities at the medial and lateral annulus were measured with TDI, and E/e' ratios were calculated separately. M-mode echocardiography provided measurements of end-diastolic dimension, interventricular septum, and posterior wall thickness at the parasternal long-axis plane near the mitral valve leaflets, averaged over three cycles. All measurements were performed offline by one experienced echocardiographer blinded to clinical and laboratory data.

SPECT myocardial perfusion imaging and ischemia definitions and quantification

MPI datasets were collected retrospectively from the hospital's electronic medical archive. All patients had previously undergone SPECT MPI at various referring centers or outpatient cardiology clinics, in accordance with standard clinical practices. Depending on individual patient characteristics, either pharmacologic or exercise-induced stress testing was performed. In total, treadmill exercise testing was performed in 355 patients, while pharmacologic stress agents were administered to 89 patients (adenosine in all cases). All scans were acquired using gated SPECT technology with technetium-99 m-labeled radiotracers, including Tc-99 m sestamibi or Tc-99 m tetrofosmin. The MPI images were not reinterpreted for the purposes of this study; all quantitative and qualitative data were extracted directly from finalized nuclear cardiology reports.

Because SPECT-MPI studies were performed at multiple centers, finalized reports were generated by board-certified nuclear cardiologists following local quality-control protocols. Studies with marked patient motion, misregistration on attenuation-corrected images, suboptimal count statistics, or gating failures were excluded. When available, attenuation correction (CT-based) and/or prone imaging were used to mitigate diaphragmatic or breast attenuation; discrepancies between non-attenuation-corrected and attenuation-corrected datasets prompted re-review. Reversible perfusion defects were accepted only when supported by a corresponding increase in stress scores (SDS) without fixed rest defects and with preserved resting wall motion on gated images, to reduce the likelihood of soft-tissue attenuation or balanced-flow artifacts.

Perfusion evaluation was based on the American Heart Association's 17-segment model of the left ventricle [10]. Each segment was scored semi-quantitatively on a 5-point scale ranging from 0 (normal perfusion) to 4 (absent perfusion) at both stress and rest phases. The Summed Stress Score (SSS), Summed Rest Score (SRS), and Summed Difference Score (SDS) were extracted directly from finalized nuclear cardiology reports. To quantify the extent of reversible ischemia, the SDS was converted into a percentage using the formula: (SDS/68) × 100, where 68 represents the maximum possible score (17 segments × 4) [11]. Myocardial ischemia was defined as a summed difference score (SDS) ≥ 3, calculated as the difference between the summed stress score (SSS) and summed rest score (SRS), based on a 17-segment, 5-point model. This threshold corresponds to a reversible perfusion defect affecting approximately ≥4–5 % of the left ventricular myocardium [12]. According to current guidelines, a reversible ischemic burden ≥10 % is considered clinically significant and may guide therapeutic decision-making. Therefore, we considered >5 % as the presence of ischemia [12], and > 10 % as clinically significant myocardial ischemia [13,14]. Based on this calculation and the relevant literature, patients were stratified according to ischemia burden as follows: <5 % reversible ischemia was considered clinically insignificant or normal, values between 5 % and 10 % represented limited ischemia, and > 10 % was regarded as clinically significant ischemia. These thresholds were used to define diagnostic groups for the analysis of coronary microvascular dysfunction (CMD).

Hypertension was considered present if resting systolic blood pressure was ≥140 mmHg, diastolic pressure was ≥90 mmHg, or if the patient was receiving antihypertensive therapy. Diabetes mellitus (DM) was defined by a fasting plasma glucose ≥126 mg/dL, a previous diagnosis by a physician, or the use of antidiabetic medications. Smoking status included individuals who currently used tobacco or had done so within the past 12 months. Body mass index (BMI) was calculated by taking the weight in kilograms and dividing it by height in meters squared.

INOCA was characterized by evidence of myocardial ischemia on SPECT myocardial perfusion imaging—specifically, a reversible ischemic burden exceeding 5 %—without significant obstructive epicardial coronary artery disease confirmed by invasive coronary angiography.

After an overnight fast of at least 8 h, all the subjects gave venous blood samples. Hematological parameters such as white blood cell count (WBC), hemoglobin (Hb), and platelet count (PLT) were measured via an automated analyzer (Sysmex XN-1000, Japan). Biochemical tests were performed with enzymatic and turbidimetric methods on a validated autoanalyzer (Roche Cobas c702, Germany).

Statistical analysis

All statistical evaluations were conducted utilizing IBM SPSS Statistics software (Version 26.0; IBM Corp., Armonk, NY, USA). The distribution characteristics of continuous variables were examined through the Shapiro–Wilk test along with visual methods, including assessment

of histograms and Q–Q plots. Data were reported as mean ± standard deviation (SD) for variables demonstrating a normal distribution, whereas non-normally distributed variables were summarized using the median and interquartile range (IQR, 25th–75th percentile). Categorical data were described by presenting their corresponding percentages.

Comparisons among the three groups categorized by the proportion of reversible ischemia detected on myocardial perfusion scintigraphy (<5 %, 5–10 %, and > 10 %) were carried out using one-way ANOVA and Kruskal–Wallis H test for continuous variables with normal distribution and for those not normally distributed, respectively. Categorical variables were evaluated with the chi-square test. When significant differences were identified between groups, post hoc pairwise analyses were performed using Bonferroni adjustment or the Mann–Whitney *U* test, on the basis of data characteristics.

To assess the correlation between PWPTs and the extent of reversible ischemia (%), Spearman's rank correlation analysis was performed. Although PWPTs exhibited approximate normal distribution across ischemia subgroups—as reflected by their presentation as mean ± SD—the distribution of ischemic burden itself was skewed and clustered toward lower percentages (<10 %). Furthermore, visual inspection of scatter plots suggested a non-linear and monotonic relationship between ischemia percentage and PWPT values. Given these considerations, Spearman's method was deemed more appropriate than Pearson's correlation, as it does not require assumptions of linearity or normality. Scatter plots with overlaid trendlines were constructed to illustrate these associations, including several clinically plausible outliers (patients with high ischemia but relatively normal PWPT).

Univariate logistic regression was performed to identify predictors of significant ischemia (>10 % reversible LV ischemia on MPS), incorporating both electrocardiographic P-wave indices, parameters of ventricular repolarization and baseline clinical characteristics that significantly differed among groups. These variables were also included in the multivariate model to adjust for potential confounders. To evaluate the goodness-of-fit of the multivariate logistic regression model, several statistical tests were performed. The Hosmer–Lemeshow test indicated good calibration ($\chi^2 = 7.15$, df = 8, $p = 0.52$), and the model demonstrated strong explanatory power as reflected by a Nagelkerke R^2 value of 0.51. The likelihood ratio chi-square test comparing the final model to the null model was statistically significant ($\chi^2 = 62.3$, $p < 0.001$), indicating that the included predictors provided a significantly better fit than the intercept-only model. Additionally, the overall classification accuracy of the model was 80.6 %, suggesting acceptable discriminatory capacity.

The ability of P-wave indices to discriminate outcomes was examined using receiver operating characteristic (ROC) analysis. Youden's index was employed to identify the optimal cutoff values, and corresponding area under the curve (AUC), sensitivity, and specificity metrics were computed.

Results

The study cohort comprised 444 consecutive subjects with INOCA undergoing coronary angiography followed by SPECT MPI. Based on quantitative evaluation of reversible perfusion defects, patients were stratified into three categories: <5 % ($n = 213$), 5–10 % ($n = 156$), and > 10 % ($n = 75$) ischemia. Statistically significant trends were observed across these groups in terms of demographic, metabolic, echocardiographic, and electrocardiographic features.

Demographic and clinical features of the study population was represented in Table 1. Age differed significantly across groups, increasing from 60.2 ± 8.3 years in the <5 % group to 60.5 ± 9.6 years in the 5–10 % group and 63.1 ± 9.3 years in the >10 % group (overall $p = 0.024$; >10 % vs <5 %, $p = 0.018$). The prevalence of DM also increased progressively (22.1 %, 30.8 %, and 41.3 %, respectively; overall $p = 0.002$; >10 % vs <5 %, $p = 0.001$). BMI showed a gradual rise from 27.2 ± 3.2 kg/m^2 in the <5 % group to 28.6 ± 3.5 kg/m^2 in the 5–10 % group and 30.4 ± 3.8 kg/m^2 in the >10 % group (overall $p = 0.016$; >10 % vs <5 %, $p = 0.017$). Median fasting glucose levels were significantly higher in

Table 1
Baseline Characteristics of Study Groups.

Variable	<5 % Ischemia (n = 213)	5–10 % Ischemia (n = 156)	>10 % Ischemia (n = 75)	p (<5 % vs 5–10 %)	p (<5 % vs >10 %)	p (5–10 % vs >10 %)	p (overall)
Age (years)	60.2 ± 8.3	60.5 ± 9.6	63.1 ± 9.3	0.081	**0.018**	**0.042**	**0.024**
BMI (kg/m^2)	27.2 ± 3.2	28.6 ± 3.5	30.4 ± 3.8	**0.043**	**0.017**	0.081	**0.016**
Male Sex (%)	58.7	59.6	62.7	0.872	0.542	0.672	0.831
DM (%)	22.1	30.8	41.3	**0.048**	**0.001**	**0.042**	**0.002**
HT (%)	60.1	64.7	62.7	0.384	0.692	0.763	0.721
Smoking (%)	31.0	35.3	46.7	**0.039**	**0.002**	**0.011**	**0.009**
Creatinine (mg/dL)	0.87 ± 0.13	0.89 ± 0.14	0.91 ± 0.15	**0.021**	0.092	0.124	0.116
Fasting Glucose (mg/dL)	104 (96–115)	108 (99–120)	114 (102–128)	0.175	**0.026**	0.185	0.076
HDL-C (mg/dL)	48 ± 6	47 ± 5	45 ± 5	0.124	**0.008**	**0.027**	**0.020**
Hb (g/dL)	13.8 ± 1.1	13.7 ± 1.0	13.5 ± 1.2	0.492	0.388	0.441	0.395
hs-CRP (mg/L)	1.8 (1.1–3.0)	2.1 (1.4–3.5)	2.6 (1.6–4.4)	**0.014**	**<0.001**	**0.019**	**<0.001**
LDL-C (mg/dL)	102 ± 14	112 ± 16	127 ± 18	**0.047**	**0.009**	**0.035**	**0.021**
PLT (10^9/L)	245 ± 52	237 ± 48	229 ± 55	0.168	**0.046**	0.084	0.067
TC (mg/dL)	195 ± 22	205 ± 25	218 ± 27	**0.038**	**0.005**	**0.028**	**<0.001**
TG (mg/dL)	145 ± 30	162 ± 33	185 ± 35	**0.042**	**0.003**	**0.025**	**0.008**
WBC (10^9/L)	6.8 ± 1.2	7.1 ± 1.4	7.6 ± 1.5	**0.038**	**0.015**	**0.042**	**0.006**
ALT (U/L)	24 (18–32)	26 (20–35)	28 (21–37)	0.198	0.111	0.327	0.219
AST (U/L)	25.8 ± 8.2	26.3 ± 8.5	26.9 ± 8.7	0.203	0.129	0.289	0.212
DT (ms)	198 ± 18	212 ± 17	223 ± 19	0.092	**0.006**	**0.037**	**0.004**
E/e' lateral	9.1 ± 1.8	10.4 ± 2.1	12.2 ± 2.2	**0.044**	**0.016**	0.082	**0.031**
LAA (cm^2)	22.5 ± 2.5	23.7 ± 2.8	25.1 ± 3.0	0.126	**0.04**	**0.024**	**0.031**
LAVI (mL/m^2)	38.2 ± 4.2	39.4 ± 4.5	40.6 ± 4.8	**0.041**	**0.012**	0.073	**0.027**
E/A ratio	0.85 ± 0.09	0.82 ± 0.08	0.79 ± 0.07	0.066	**0.047**	0.157	**<0.01**
LVEF (%)	62.8 ± 5.5	65.9 ± 7.3	64.4 ± 6.1	0.082	0.078	0.126	0.097

WBC: White Blood Cell Count; Hb: Hemoglobin; hs-CRP: High-sensitivity CRP; PLT: Platelet Count; TC: Total Cholesterol; LDL-C: Low-density Lipoprotein Cholesterol; HDL-C: High-density Lipoprotein Cholesterol; TG: Triglycerides; LAVI: Left Atrial Volume Index; LAA: Left Atrial Area; DT: Deceleration Time; BMI: Body Mass Index; HT: Hypertension; DM: Diabetes Mellitus; AST: Aspartate Transaminase; ALT: Alanine Transaminase. LVEF: Left Ventricular Ejection Fraction.
Note: Data are presented as mean ± standard deviation or median (25th–75th percentile) where appropriate. Bold values indicate statistically significant comparisons ($p < 0.05$).

the >10 % group (114 [102–128] mg/dL) compared to the <5 % group (104 [96–115] mg/dL; $p = 0.026$). Serum triglycerides increased from 145 ± 30 mg/dL to 185 ± 35 mg/dL across the groups (overall $p = 0.008$). LDL cholesterol followed a similar trend (overall $p = 0.021$). hs-CRP also showed a stepwise elevation, with median values of 1.8 [1.1–3.0] mg/L in the <5 % group, 2.1 [1.4–3.5] mg/L in the 5–10 % group, and 2.6 [1.6–4.4] mg/L in the >10 % group (overall $p < 0.001$; >10 % vs <5 %, $p < 0.001$).

Regarding echocardiographic parameters, diastolic dysfunction markers were more pronounced in the >10 % ischemia group. Lateral E/e' ratio was 9.1 ± 1.8 in the <5 % group, 10.6 ± 2.0 in the 5–10 % group, and 12.2 ± 2.2 in the >10 % group ($p = 0.016$; >10 % vs <5 %, $p = 0.003$). DT progressively increased across groups (198 ± 18 ms, 211 ± 17 ms, and 223 ± 19 ms, respectively; $p = 0.006$). LAVI showed a similar trend: 38.2 ± 4.2 mL/m^2 in the <5 % group, 39.4 ± 4.4 mL/m^2 in the 5–10 % group, and 40.6 ± 4.8 mL/m^2 in the >10 % group ($p = 0.012$). No significant differences were observed in LVEF among the groups ($p = 0.211$).

Electrocardiographic P-wave and ventricular repolarization indices were compared in Table 2. P-wave indices exhibited statistically significant stepwise increases in association with ischemia burden. PWPT-DII increased from 52 ± 6 ms in the <5 % group to 58 ± 7 ms in the 5–10 % group and 63 ± 9 ms in the >10 % group ($p < 0.001$; >10 % vs <5 %, $p < 0.001$). PWPT-V1 followed a similar trend (53 ± 7 ms, 56 ± 7 ms, and 60 ± 6 ms, respectively; $p < 0.001$). PWdur rose from 102 ± 8 ms in the <5 % group to 107 ± 7 ms and 112 ± 6 ms in the higher groups ($p < 0.001$) (Fig. 2). PWd increased from 43 ± 6 ms to 49 ± 7 ms and 55 ± 8 ms, respectively ($p < 0.001$). PWTFV1 was also significantly higher in the >10 % group (38 ± 9 mm·ms) than in both the 5–10 % (30 ± 8 mm·ms) and < 5 % groups (26 ± 8 mm·ms) ($p < 0.001$). Additional ventricular repolarization parameters were compared across ischemia subgroups to evaluate their association with ischemic burden. Although the mean QT intervals showed a gradual increase from <5 % to >10 % ischemia groups (375 ± 26 ms, 385 ± 23 ms, and 388 ± 22 ms, respectively), the difference did not reach statistical significance ($p = 0.143$). In contrast, QTc intervals were significantly longer in patients with >10 % ischemia compared to those with <5 % (432 ± 20 ms vs. 424 ± 19 ms; $p = 0.002$), with an overall p value of 0.018. TPE duration also increased across groups and was significantly prolonged in the >10 % group compared to the <5 % group (83 ± 10 ms vs. 76 ± 8 ms; $p = 0.014$). While TPE/QT ratios were similar across all subgroups ($p = 0.246$), the TPE/QTc ratio was significantly higher in patients with >10 % ischemia (0.21 ± 0.03) than in both the <5 % (0.18 ± 0.03; $p = 0.003$) and 5–10 % ischemia groups (0.19 ± 0.03; $p = 0.020$). Additionally, QT dispersion exhibited a stepwise and statistically significant increase with ischemia severity (36 ± 7 ms in <5 %, 42 ± 8 ms in 5–10 %, and 49 ± 9 ms in >10 %; $p < 0.001$), with all pairwise comparisons showing significant differences.

In the correlation analysis, a significant positive association was observed between the extent of reversible ischemia and both PWPT-DII and PWPT-V1. Spearman's rank correlation coefficient demonstrated a moderate monotonic relationship between ischemic burden and PWPT-DII ($r = 0.32$, $p < 0.001$), as well as PWPT-V1 ($r = 0.42$, $p < 0.001$). These findings suggest that higher degrees of perfusion abnormalities on SPECT-MPI are associated with prolonged atrial conduction times, particularly in lead DII. Scatter plots were generated to visually depict these associations and confirmed the upward trends in PWPTs with increasing ischemia percentage (Fig. 3). Notably, a small number of patients with elevated ischemia burden exhibited PWPTs within the normal range, highlighting the biological variability of conduction parameters in INOCA and the potential influence of individual microvascular reserve. Moreover, visual dispersion in the scatterplot reflects the continuous nature of the variables; ROC-based cutoffs are derived to optimize overall discrimination, which does not require perfect alignment with quadrant separation in the raw bivariate plot.

In univariate logistic regression analysis, PWPT-DII (odds ratio [OR] 1.20; 95 % confidence interval [CI] 1.14–1.25; $p < 0.001$), PWPT-V1 (OR 1.16; 95 % CI 1.12–1.20; $p < 0.001$), age (OR 1.05; 95 % CI 1.02–1.08; $p = 0.021$), DM (OR 2.45; 95 % CI 1.30–4.62; $p = 0.006$), and lateral E/e' (OR 1.97; 95 % CI 1.68–2.31; $p = 0.014$) were associated with significant myocardial ischemia (>10 %). Multivariate model, after adjustment for clinical and echocardiographic confounders, showed that PWPT-DII (OR 1.15; 95 % CI 1.08–1.23; $p < 0.001$) and PWPT-V1 (OR 1.10; 95 % CI 1.03–1.17; $p < 0.001$) remained independently associated with significant ischemia. Age (OR 1.04; 95 % CI 1.01–1.07; $p = 0.018$), DM (OR 1.88; 95 % CI 1.05–3.36; $p = 0.029$), lateral E/e' (OR 1.74; 95 % CI 1.07–2.81; $p = 0.026$), and TPE/QTc (OR 1.09; 95 % CI 1.02–1.18; $p = 0.008$) and QTd (OR 1.14; 95 % CI 1.05–1.25; $p = 0.002$) also remained significant in the multivariate model (Table 3).

ROC analysis showed that PWPT-DII had the highest discriminative value for identifying >10 % ischemia, with an AUC of 0.83 (95 % CI 0.79–0.87). The optimal cutoff value was 60.3 ms with a sensitivity of 81.3 % and a specificity of 71.5 %. PWPT-V1 yielded a slightly smaller AUC of 0.76 (95 % CI 0.70–0.82), with a cutoff of 58.6 ms providing 61.3 % sensitivity and 84.6 % specificity (Fig. 4).

Table 2
Comparison of P-wave Indices Across Ischemia Groups.

	<5 % Ischemia	5–10 % Ischemia	>10 % Ischemia	p (<5 % vs 5–10 %)	p (<5 % vs >10 %)	p (5–10 % vs >10 %)	p (overall)
PWdur (ms)	102 ± 8	106 ± 9	112 ± 6	0.142	**<0.001**	**0.031**	**0.013**
PTFV1 (mm·ms)	26 (21–31)	30 (25–35)	38 (32–44)	0.091	**<0.001**	**0.048**	**0.041**
PWd (ms)	43 ± 6	48 ± 6	55 ± 8	0.062	**<0.001**	**0.017**	**0.007**
Pmin (ms)	58 ± 6	59 ± 7	60 ± 6	0.417	0.214	0.495	0.178
Pmax (ms)	94 ± 8	98 ± 8	104 ± 9	0.096	**<0.001**	**0.039**	**0.024**
PWPT-D2 (ms)	52 ± 6	56 ± 9	63 ± 9	**0.021**	**<0.001**	**<0.001**	**<0.001**
PWPT-V1 (ms)	53 ± 7	57 ± 5	60 ± 6	**<0.001**	**<0.001**	**<0.037**	**<0.001**
Heart Rate (bpm)	71 ± 10	73 ± 9	75 ± 8	0.128	0.069	0.101	0.084
RR Interval (ms)	845 ± 105	812 ± 98	790 ± 91	0.149	0.071	0.095	0.078
QT Interval (ms)	375 ± 26	385 ± 23	388 ± 22	0.114	0.088	0.174	0.143
QTc Interval (ms)	424 ± 19	427 ± 18	432 ± 20	0.086	**0.002**	**0.013**	**0.018**
TPE (ms)	76 ± 8	80 ± 9	83 ± 10	0.049	**0.014**	0.073	**0.037**
TPE/QT	0.20 ± 0.03	0.21 ± 0.03	0.21 ± 0.04	0.117	0.133	0.841	0.246
TPE/QTc	0.18 ± 0.03	0.19 ± 0.03	0.21 ± 0.03	0.062	**0.003**	**0.020**	**0.008**
QTd (ms)	36 ± 7	42 ± 8	49 ± 9	**0.004**	**<0.001**	**0.011**	**<0.001**

PWdur: P-wave duration; PTFV1: P-wave terminal force in lead V1; PWd: P-wave dispersion; Pmin: Minimum P-wave duration; Pmax: Maximum P-wave duration; PWPT-D2: P-wave peak time in lead DII; PWPT-V1: P-wave peak time in lead V1; QT: QT interval; QTc: Corrected QT interval (Bazett's formula); RR: RR interval; bpm: beats per minute; TPE, T wave peak-to-end time; QTd, QT dispersion.

Note: Data are presented as mean ± standard deviation or median (25th–75th percentile) where appropriate. Bold values indicate statistically significant comparisons ($p < 0.05$).

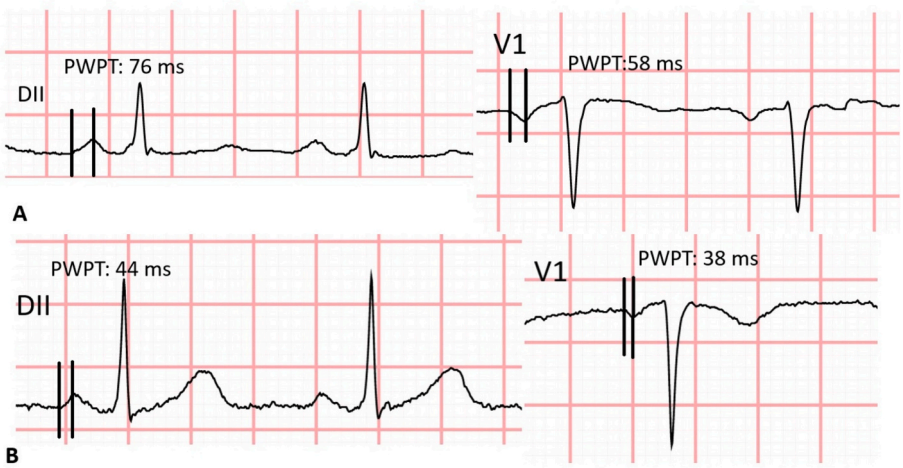

Fig. 2. A) ECG sample of a patient with SPECT-MPI ischemia >10 %. **B)** ECG sample of a patient with SPECT-MPI ischemia <5 %.

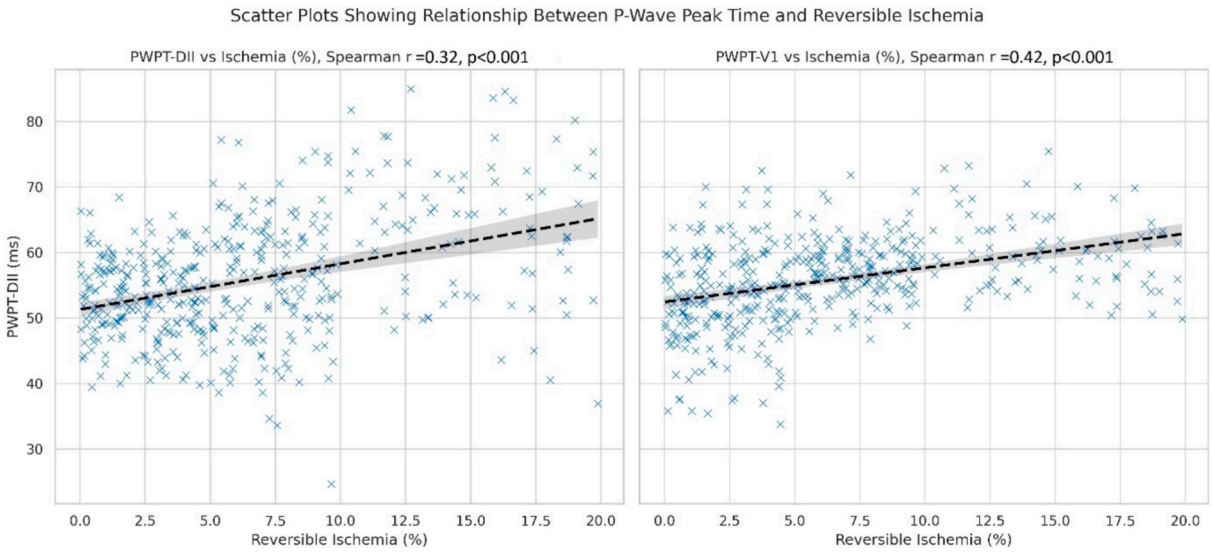

Fig. 3. Spearman correlation scatter plots demonstrating a significant positive correlation between the extent of ischemia and both PWPT-DII and PWPT-V1.

Discussion

Current study investigated the association between electrocardiographic P-wave indices and the presence of myocardial ischemia in INOCA patients. Our findings demonstrate that prolonged PWPT, particularly in leads DII and V1, is independently associated with a higher burden of reversible myocardial perfusion defects as quantified by SPECT MPI. Importantly, PWPT-DII exhibited a stronger predictive capacity for significant ischemia compared to PWPT-V1, both in terms of ROC performance and logistic regression outcomes. In addition to PWPTs, traditional clinical and echocardiographic predictors such as age, the presence of DM, and elevated E/e' ratio also emerged as independent predictors of significant ischemia. These results suggest that atrial conduction delays, as reflected by prolonged PWPT, may serve as a non-invasive ECG marker of microvascular ischemia in INOCA patients. In this regard, our study adds to the growing body of literature by emphasizing the diagnostic potential of ECG-based parameters, together with the subclinical left ventricular diastolic dysfunction and metabolic comorbidities, and highlight the utility of combining clinical, echocardiographic, and electrocardiographic markers to identify patients at increased risk of myocardial ischemia in the absence of obstructive CAD.

INOCA is a common yet often underdiagnosed clinical entity. Epidemiologic data suggest that among patients undergoing elective coronary angiography for angina, 50–70 % of women and 30–50 % of men exhibit no obstructive CAD, despite having demonstrable myocardial ischemia [15]. Findings from the Women's Ischemia Syndrome Evaluation study have estimated that approximately 3–4 million individuals in the United States may be affected by INOCA [16]. Additionally, the ISCHEMIA trial documented that 13.2 % of cases with moderate-to-severe myocardial ischemia on non-invasive testing had non-obstructive coronary arteries on angiography [17]. These figures underscore the clinical importance of INOCA and justify the need for further investigation into its pathophysiology and non-invasive diagnostic markers. CMD has emerged as the predominant pathophysiological mechanism underlying ischemia with INOCA. CMD is defined by structural and functional abnormalities within the coronary microcirculation—such as impaired vasodilator capacity, enhanced endothelial dysfunction, arteriolar remodeling, and inflammation—that collectively disrupt coronary blood flow [18]. Recent expert consensus emphasizes that CMD is the most common mechanism in INOCA, frequently coexisting with vasospastic mechanisms, and directly correlates with symptoms, ischemic burden, and adverse outcomes [1]. In particular, impaired CFR measured invasively or via PET is present in approximately 50–60 % of INOCA patients [19].

Table 3
Logistic regression analysis to predict >10 % LV ischemia in MPI.

Variable	OR (95 % CI) (Univariate)	p (Univariate)	OR (95 % CI) (Multivariate)	p (Multivariate)
PWd	1.24 (1.18–1.30)	**0.032**	1.08 (0.99–1.17)	0.074
PTFV1	1.19 (1.15–1.24)	**0.041**	1.07 (0.97–1.19)	0.182
PWdur	1.14 (1.10–1.18)	**0.038**	1.07 (0.98–1.17)	0.116
PWPT-V1	1.16 (1.12–1.20)	**<0.001**	1.13 (1.08–1.18)	**<0.001**
PWPT-DII	1.20 (1.14–1.25)	**<0.001**	1.17 (1.09–1.25)	**<0.001**
QT	1.01 (0.99–1.02)	0.282	–	–
QTc	1.02 (0.99–1.05)	0.110	–	–
TPE	1.03 (0.98–1.08)	0.156	–	–
TPE/QT	1.07 (0.91–1.25)	0.289		
TPE/QTc	1.12 (1.05–1.21)	**<0.001**	1.09 (1.02–1.18)	**0.008**
QTd	1.15 (1.08–1.23)	**<0.001**	1.14 (1.05–1.25)	**0.002**
E/A	1.05 (0.98–0.12)	0.144	–	–
LAA	1.27 (1.16–1.40)	**0.035**	1.04 (0.97–1.12)	0.230
E/e' lateral	1.97 (1.68–2.31)	**0.014**	1.74 (1.07–2.81)	**0.026**
DT	1.07 (1.05–1.09)	**0.039**	1.01 (0.94–1.02)	0.239
TG	1.03 (1.02–1.03)	**0.027**	0.98 (0.92–1.04)	0.412
Hs-CRP	4.60 (3.20–6.61)	**0.004**	1.48 (0.91–2.39)	0.110
BMI	1.19 (1.11–1.28)	**0.048**	1.03 (0.84–1.11)	0.143
TC	1.02 (1.01–1.03)	**0.044**	0.98 (0.89–1.01)	0.411
LAVI	1.11 (1.05–1.17)	**0.019**	1.03 (0.99–1.07)	0.120
WBC	1.38 (1.14–1.67)	**0.025**	1.03 (0.97–1.09)	0.248
Age	1.05 (1.02–1.08)	**0.021**	1.04 (1.01–1.07)	**0.018**
DM	2.45 (1.30–4.62)	**0.006**	1.88 (1.05–3.36)	**0.029**
Smoking	1.12 (0.91–1.38)	0.176	–	–
Female gender	1.34 (0.81–2.23)	0.066	–	–
HT	1.32 (0.77–2.25)	0.059	–	–

Model fit statistics: The multivariate logistic regression model demonstrated good calibration (Hosmer–Lemeshow $\chi^2 = 7.15$, df = 8, p = 0.52), strong explanatory power (Nagelkerke $R^2 = 0.51$), and significant overall model fit (Likelihood Ratio $\chi^2 = 62.3$, $p < 0.001$). The model's classification accuracy was 80.6 %.

Advancing age and DM have consistently been related to a greater likelihood of myocardial ischemia in INOCA. These factors contribute to CMD through mechanisms such as endothelial dysfunction, impaired vasodilatory capacity, and increased arterial stiffness [20]. Additionally, both aging and DM are well-established contributors to LV diastolic dysfunction, a widespread finding in subjects with INOCA [7]. Accumulating evidence suggests that chronic exposure to subendocardial ischemia in patients with INOCA may precipitate progressive myocardial injury, ultimately promoting diffuse interstitial fibrosis, increased myocardial stiffness, and subsequent diastolic dysfunction [21]. This association is supported by prior studies demonstrating that INOCA frequently coexists with preserved ejection fraction heart failure phenotypes, in which diastolic abnormalities such as elevated E/e' ratios are prominent [7,22]. In a study by Kong et al. [23], quantitative analysis using cardiovascular magnetic resonance feature tracking in INOCA patients demonstrated reduced regional diastolic strain rates, highlighting subtle diastolic impairment not accompanied by global systolic dysfunction. Similarly, a larger meta-analysis encompassing 14 studies, echocardiographic LAVI and E/e' were found to be elevated significantly in patients with CMD as compared with the cases without CMD [24]. Our findings align with this pathophysiological link, as both age and diabetes, along with increased E/e', independently predicted the presence of significant reversible ischemia in our cohort. These results underscore the importance of recognizing INOCA not only as an ischemic condition, but also as a marker of systemic cardiometabolic and functional cardiac derangements.

Recent investigations have increasingly underlined the utility of PWPT as a sensitive ECG marker for atrial conduction abnormalities and arrhythmogenic risk in ischemic cardiovascular conditions. In a study conducted by Öz et al. [25], involving patients with acute ischemic stroke, PWPT-DII was identified as an independent predictor of paroxysmal atrial fibrillation (PAF). Within this analysis, a cutoff value of 68.5 ms yielded a sensitivity of 82.4 % and a specificity of 75.0 %. Furthermore, their multivariate analysis revealed that PWPT-DII (OR: 1.34, 95 % CI: 1.15–1.56, $p < 0.001$) exhibited a stronger association with PAF compared to PWPT-V1 (OR: 1.12, 95 % CI: 1.02–1.22, $p = 0.010$). Similarly, our study demonstrated that increased PWPT values, particularly in lead DII, be independently associated with reversible myocardial ischemia in INOCA patients, as detected by SPECT-MPI. Notably, the odds ratio for PWPT-DII in our logistic regression model was higher than that for lead V1, supporting the notion that atrial conduction delay in this lead may more closely reflect ischemia-related atrial remodeling. These findings reinforce the potential of lead-specific PWPT as a low-cost, non-invasive surrogate marker not only for arrhythmic risk but also for underlying myocardial ischemia in populations where traditional obstructive coronary disease is absent.

P-wave indices have previously been identified as valuable non-invasive markers of atrial conduction abnormalities linked to myocardial ischemia. In a study by Yıldırım et al. [26], Pmax and PWd were found to be significantly elevated in patients with chronic coronary syndrome (CCS), with the most prominent prolongation observed during morning hours, supporting the hypothesis of a circadian variation in ischemia-induced atrial conduction heterogeneity. Similarly, Dilaveris et al. [27] demonstrated that both Pmax and PWd increased during spontaneous anginal episodes in patients with angiographically proven CCS, particularly in those exhibiting ST-segment depressions in multiple ECG leads, indicative of diffuse ischemia. More recently, Bayam et al. [9] investigated PWPT in non-ST elevation myocardial infarction cases and revealed a significant and independent association between PWPT values and Gensini scores (OR: 1.07, 95 %CI: 1.02–1.13; $p = 0.002$), indicating a greater burden of myocardial ischemia and atherosclerosis. In a subsequent study by Çağdaş et al. [8], PWPT-DII emerged as an independent predictor of angiographic no-reflow in STEMI patients (cut-off: 67.4 ms; sensitivity 90.9 %, specificity 58.8 %, AUC: 0.778), underscoring its potential as a surrogate marker of CMD and perfusion failure. These studies collectively emphasize the sensitivity of P-wave indices, particularly PWPT, to underlying ischemic conditions across diverse clinical contexts, and underscore the dynamic nature of ischemia-related conduction disturbances and their potential arrhythmogenic implications. Expanding upon this pathophysiological framework, our study evaluated P-wave indices—specifically PWPTs—in a cohort of patients with INOCA. We found that PWPT-DII and —V1 were independently associated with a greater burden of reversible ischemia on SPECT-MPI.

Beyond their potential utilities in patients with obstructive CAD, some P-wave indices were also investigated as potential ECG markers of atrial electrical remodeling in patients with non-obstructive CAD. For example, Keleşoğlu et al. [6] demonstrated that PWd and Pmax be

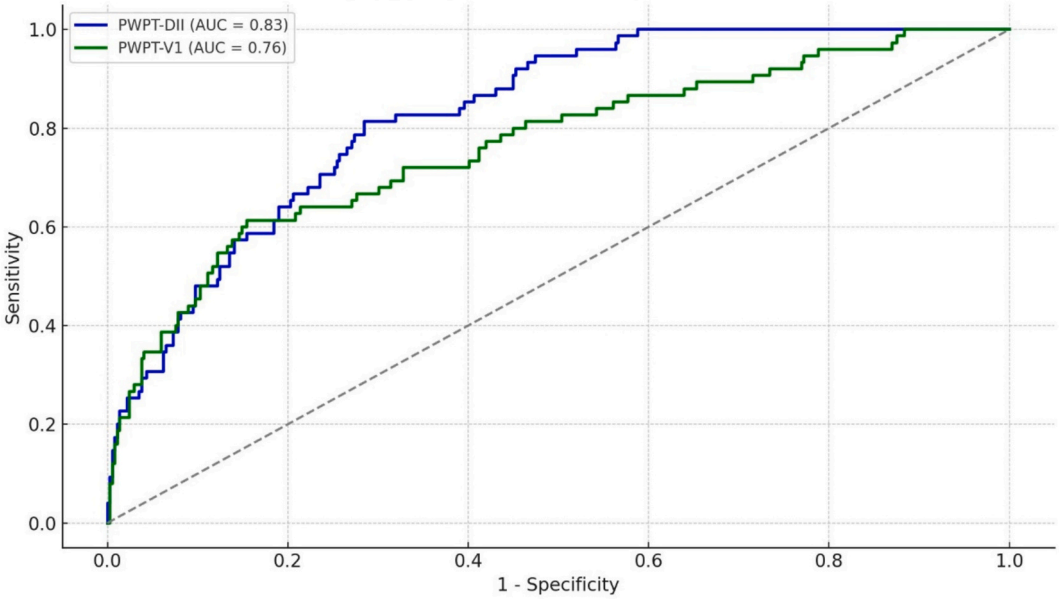

Fig. 4. ROC curves with diagnostic cutoff values of PWPT-DII and PWPT-V1.

elevated significantly in angina with non-obstructive coronary arteries (ANOCA) cases compared with healthy subjects, suggesting an escalated atrial arrhythmia risk like AF in this population. Similarly, Aslan et al. [7] reported that both PWd and Pmax were significantly greater in patients having coronary slow-flow phenomenon compared to healthy individuals, implying that these parameters may reflect subclinical myocardial ischemia or conduction heterogeneity even in the absence of obstructive lesions. These findings align with the present study's results, which revealed that prolonged PWPTs in certain ECG leads were independently associated with the extent of reversible ischemia on SPECT-MPI in INOCA patients. Although these studies have explored alterations in some P-wave indices among patients with non-obstructive coronary conditions, important distinctions exist in study populations. For example, Keleşoğlu et al. investigated only symptomatic patients without documented myocardial perfusion abnormalities—an ANOCA cohort—limiting the ability to directly correlate P-wave changes with objective evidence of ischemia. Likewise, Aslan et al. [7] conducted a study examining individuals diagnosed with the coronary slow flow phenomenon—a unique clinical condition marked by delayed filling of the epicardial coronary arteries despite the absence of significant luminal stenosis, and not always accompanied by perfusion abnormalities on imaging studies. In contrast, our study specifically included patients with SPECT-MPI–documented reversible ischemia in the absence of epicardial coronary stenosis, representing a well-defined INOCA population. By assessing P-wave indices in this objectively characterized ischemic subgroup, our findings may offer novel evidence supporting the association between atrial conduction disturbances—particularly prolonged PWPTs—and probable CMD. This distinction underscores the value of ECG-derived atrial parameters as potential surrogate markers of ischemia in INOCA, beyond symptom-based classification alone. These observations reinforce the notion that ischemia-induced atrial conduction delay is not exclusive to obstructive CAD but may also reflects microvascular pathology. Extending this concept, our study demonstrates that in a well-defined INOCA population, prolongation of PWPTs in specific ECG leads significantly corresponds with reversible ischemia on SPECT-MPI. These findings underscore PWPT's potential as a simple, widely available marker of CMD in patients without obstructive epicardial lesions.

Another issue is that emerging evidence supports that atrial conduction parameters such as PWPT and electromechanical delay may even be altered even in the absence of overt ventricular diastolic dysfunction. For instance, in patients with mild LV diastolic impairment but normal LA volume and filling pressures, atrial conduction delays did not correlate directly with diastolic indices, suggesting early atrial electrical remodeling occurs interdependently [28]. Similarly, prolonged PWPT has been demonstrated in patients with severe coronary artery disease, irrespective of diastolic dysfunction status [29]. These findings indicate that PWPT prolongation may reflect early atrial electrophysiological changes secondary to microvascular ischemia and atrial stretch—potentially detectable before diastolic dysfunction becomes apparent. On the other hand, E/E' lateral and EDT significantly increased, whereas E/A significantly decreased across increasing reversible LV ischemia subgroups as evident in Table 1 in our study. Moreover, LAA and LAVI significantly increased in the ischemia subgroups with >10 %, supporting the deterioration in the LV diastolic dysfunction and possible atrial ischemia.

During myocardial ischemia, prolongation of the PWPT is believed to reflect underlying abnormalities in atrial conduction. Repeated episodes of subclinical myocardial ischemia provoke localized hypoxia within the atrial myocardium, leading to oxidative stress, inflammatory cell infiltration, and subsequent structural alterations including interstitial fibrosis. These changes disrupt the uniform propagation of electrical impulses across the atrial tissue, resulting in prolonged atrial conduction times, leading to slowed depolarization, and regional heterogeneity in atrial conduction. This is particularly evident in surface ECG leads such as DII and V1, which represent the lateral and anterior-septal atrial regions, respectively. In addition, ischemia provokes an inflammatory cascade marked by elevated concentrations of cytokines like TNF-α and IL-6. These mediators can influence the expression of gap junction proteins, including connexin-40 and connexin-43, ultimately impairing intercellular electrical conduction [30,31]. CMD, common in INOCA patients, contributes to subendocardial hypoperfusion and atrial tissue hypoxia, fostering both electrical instability and structural remodeling, including fibrosis [31]. Furthermore, oxidative stress caused by reactive oxygen species and mitochondrial dysfunction during ischemia further disrupt ionic homeostasis and prolong conduction times [32]. These pathophysiological changes culminate in a prolonged PWPT, even in the absence of obstructive CAD. This mechanistic framework supports the clinical utility of PWPT as a non-invasive indicator of atrial involvement in ischemic heart disease, including INOCA.

The present study also investigated ventricular repolarization indices derived from standard 12-lead ECGs, including QT, QTc, TPE, TPE/QT, TPE/QTc, and QTd. While QT and QTc intervals have long been established markers of repolarization delay, their diagnostic utility in INOCA remains uncertain. In our cohort, QTc and TPE durations were significantly prolonged in patients with >10 % ischemia; however, only TPE/QTc and QTd demonstrated consistent and independent associations with ischemia severity in both univariate and multivariate regression analyses. TPE/QTc, by accounting for heart rate variability, may more accurately reflect transmural dispersion of repolarization and regional heterogeneity in myocardial recovery times. QTd, which estimates spatial variation in repolarization across different myocardial territories, has similarly been linked to microvascular dysfunction and subclinical ischemia. These findings suggest that specific repolarization parameters, particularly TPE/QTc and QTd, may serve as simple yet powerful non-invasive markers of microvascular ischemic burden in patients with INOCA.

As a future perspective, integration of PWPTs into existing risk prediction models of advanced machine learning and artificial intelligence (AI) algorithms could improve early identification and stratification of patients with CMD, and also combining them with advanced diagnostic tools—such as CFR assessment or cardiac MRI—may enhance the precision of non-obstructive ischemia diagnosis. Automated ECG interpretation platforms could allow for rapid and accurate identification of subtle atrial conduction abnormalities that may signal underlying microvascular ischemia, particularly in INOCA populations. Moreover, combining P-wave metrics with other non-invasive parameters in predictive modeling could improve early risk stratification and personalized treatment planning. Investigating whether therapeutic modulation of CMD leads to improvements in these P-wave indices and subsequent outcomes may offer novel directions for personalized treatment in this underrecognized population.

Future large-scale, multicenter prospective studies utilizing AI-based approaches with more varied patient groups and are needed to verify these findings and assess their predictive value for cardiovascular events, including heart failure with preserved LVEF and AF.

This study has several important limitations. First of all, retrospective and observational design inherently limits the study's capability to establish causality and may be subject to selection and information bias. Data were extracted from hospital records without prospective standardization, which could influence data consistency and interpretation. For this reason, future multicenter studies are warranted to validate our findings. Second, SPECT MPI was not performed in a single center, but rather across multiple external institutions, with potential variability in image acquisition, stress protocols, radiotracer usage, and reporting standards. Although ischemia quantification was based on standardized visual scoring (17-segment model) and percent ischemic burden derived from SDS, this variability could still affect the reproducibility of MPI findings. Moreover, despite applying pragmatic exclusion criteria (motion, misregistration, poor counts, gating failure) and relying on standardized finalized reports, residual attenuation or interpretive artifacts cannot be completely excluded. Thus, misclassification bias remains possible, and our estimates of ischemic burden should be interpreted with this constraint in mind Third, definitive diagnosis of CMD requires invasive or advanced non-invasive testing (e.g., CFR or endothelial function assessment), which was not feasible in this retrospective cohort. Consequently, although our study population fits the clinical profile of INOCA, we cannot exclude the contribution of other mechanisms such as vasospasm or predominant endothelial dysfunction. This limitation introduces a risk of potential diagnostic misclassification, as some patients may have been incorrectly categorized as having microvascular ischemia solely based on perfusion imaging without confirmatory functional testing. Fourth, the lack of longitudinal follow-up limits our capacity to evaluate the prognostic significance of the identified P-wave abnormalities and the extent of ischemic burden. Fifth, we also acknowledge that concomitant atrial ischemia or inflammation may also be present together with the deteriorations in the LV diastolic functions in our study population. However, we did not directly assess this issue using cardiac MRI or atrial strain imaging in an attempt to elucidate whether such mechanisms contribute directly to atrial conduction delay in INOCA patients. Sixth, the study population was derived from a single regional cohort in Türkiye, which may limit the generalizability of the findings to other ethnic or geographic populations. Moreover, we acknowledge that the study did not include a completely ischemia-negative control group. However, patients with <5 % ischemia were used as a reference category, consistent with prior imaging-based ischemia stratification models [33]. Lastly, while we performed multivariate adjustment for baseline differences between groups, residual confounding due to unmeasured factors such as medication use (e.g., antiplatelet agents, antihypertensives, or vasoactive drugs), autonomic nervous system activity, or hormonal influences cannot be entirely ruled out. While lack of medications used represents a potential limitation, our multivariate models adjusted for key comorbidities (hypertension, diabetes) that largely determine these medication regimens, and the consistent association between P-wave indices and ischemia burden across clinical subgroups suggests robustness of our findings. Future prospective studies should incorporate detailed medication recording and standardized washout protocols where feasible to further isolate these relationships.

Conclusion

Specific P-wave parameters, especially PWPT-DII and PWPT-V1, show independent associations with the presence of clinically relevant myocardial ischemia in INOCA patients, as demonstrated by SPECT MPI. These findings suggest that atrial electrophysiological alterations, as reflected in surface ECG measurements, may serve as accessible and non-invasive markers of myocardial ischemia in this population. We emphasize that our results are exploratory and hypothesis-generating rather than definitive, and larger, multicenter studies including broader ECG profiling and assessment of various cardiac pathologies are warranted to validate and expand upon our observations.

CRediT authorship contribution statement

Muhammet Salih Ateş: Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Erdoğan Sökmen:** Supervision, Software, Resources, Methodology, Investigation, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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