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ORIGINAL ARTICLE

Increased sensitivity of prolonged P-wave during exercise stress test in detection of angiographically documented coronary artery disease

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Abstract

Background: *A retrospective study was designed to investigate P-wave duration changes in exercise stress test (EST) for the prediction of angiographically documented substantial coronary artery disease (CAD).*

Methods: *We analyzed 265 cases of patients, who underwent EST and subsequently coronary angiography. Analysis of P-wave duration was performed in leads II, V_5 at rest, and in the recovery period.*

Results: *The sensitivity and specificity for the isolated ST-segment depression were only 31% and 76%, respectively. The combination of ST-depression with other exercise-induced clinical and electrocardiographic abnormalities (chest pain, ventricular arrhythmia, hypotension, left bundle branch block) was characterized by 41% sensitivity and 69% specificity. The combination of abnormal recovery P-wave duration (≥ 120 ms) with ST-depression and other exercise-induced abnormalities had 83% sensitivity but only 20% specificity. Combined analysis of increased delta P-wave duration, ST-depression and other exercise-induced abnormalities had 69% sensitivity and 42% specificity. Sensitivity and specificity of the increase in delta P-wave duration for left CAD was 69% and 47%, respectively, and for 3-vessel CAD 70% and 50%, respectively. The presence of arterial hypertension negatively influenced the prognostic value of P-wave changes in the stress test.*

Conclusions: *The results of the study show that an addition of P-wave duration changes assessment to ST-depression analysis and other exercise-induced abnormalities increase sensitivity of EST, especially for left CAD and 3-vessel coronary disease. We have also provided evidence for the negative influence of the presence of arterial hypertension on the predictive value of P-wave changes in the stress test.* (Cardiol J 2017; 24, 2: 159–166)

Key words: coronary angiography, coronary disease, electrocardiography, P-wave, exercise stress test

Introduction

An analysis of the ST-segment during exercise stress test (EST) is an acknowledged method for myocardial ischemia detection with sensitivity and specificity for coronary disease up to 50% and 90%, respectively [1–3]. According to current guidelines for the diagnosis of stable coronary artery disease (CAD), EST is recommended, especially for intermediate-risk patients [1–4].

The assessment of P-wave parameters is a substantial element of both resting and stress electrocardiography. The prolongation and inhomogeneous propagation of electrical impulses through the muscle of the atrial wall with subsequent changes of the P-wave duration (PWD) and P-wave dispersion were found to increase the risk of paroxysmal and recurrent atrial fibrillation [5, 6]. Chronic arterial hypertension results in left atrium enlargement and left ventricular (LV) hypertrophy and, in effect, was shown to widen P-wave ≥ 120 ms on electrocardiographic tracings [7]. An increased amount of data also provides evidence for PWD and dispersion changes in obesity and in patients with chronic obstructive sleep syndrome [8, 9].

In several studies, widened P-wave was regarded as an easily quantifiable morphophysiologic parameter of LV diastolic dysfunction and an early marker of myocardial ischemia [10, 11]. Myrianthefs et al. [12] reported that during coronary angioplasty P-wave dispersion was higher and correlated with the severity of the coronary artery stenosis. This thesis was supported by other authors [13–15]. To date, the usefulness of P-wave parameters as an identification of ischemia during EST has been assessed in only a few observations.

The objective of the present study was to assess the significance of the estimation of PWD in EST for the prediction of substantial coronary stenoses documented by coronary angiography. Based on the abovementioned data, the study was also planned to discover whether the presence of arterial hypertension and obesity affects EST PWD duration changes and how the presence of these comorbidities changes the predictive value of P-wave parameters for CAD diagnosis.

Methods

For the present study, we retrospectively enrolled a cohort of 265 patients (inpatients; 177 male; mean age: 60.75 ± 9.9 years), who from 2009 to 2011 underwent exercise stress tests for CAD diagnosis and subsequently, but not longer than 6 months later, coronary angiography in the Department of Cardiology, Brodnowski Hospital. The experimental protocol was approved by the Human Research Ethics Committee of the Warsaw Medical University (KB/191/2012). Patients with any of the following were excluded from the study: a medical history of atrial fibrillation, with a pacemaker rhythm, atrioventricular or intraventricular conduction disturbances (except from the left bundle branch block [LBBB] that appeared on EST),

or significant motion artifacts in the electrocardiography that made it impossible to estimate P-wave parameters precisely. Demographic and clinical data were obtained from the medical histories of patients and the database in the Ergometry Laboratory. The following information was noted: age, gender, weight, height, arterial hypertension, resting transthoracic echocardiographic parameters (ejection fraction, the LV diastolic diameter, the presence of LV hypertrophy), and current pharmacotherapy. Body mass index (BMI) was calculated as the ratio of weight in kilograms divided by the square of height in meters.

A treadmill exercise stress test was performed in the presence of an experienced physician using a GE CASE Version 6.1 (GE Medical Systems, Freiburg, Germany) and the Bruce protocol was applied for all patients [16]. The test was described as "ischemic" according to the presence of acknowledged clinical and electrocardiographic abnormalities, such as chest pain, horizontal or downsloping ST-segment depression ≥ 0.10 mV (1 mm) or ST-segment elevation ≥ 1 mm at the J point plus 60 ms, emergence of ventricular arrhythmia, exercise-induced hypotension, exercise-induced LBBB at a heart rate < 125 bpm [17].

An analysis of PWD was performed, according to the procedure described above, at resting conditions (resting PWD) and in the first minute of the recovery period (recovery PWD) when the heart rate was < 140 bpm, while the patient was standing on the treadmill, according to the protocol described before [14, 16]. PWD was recognized as abnormal when PWD ≥ 120 ms. All electrocardiograms were recorded with a speed of 25 mm/s and with an amplitude of 1 mV/cm. Changes in the P-wave parameters were estimated (computer-assisted assessment) in leads II and V_5 by two independent investigators blinded to the results of both EST and coronary angiography according to the procedure described previously by Maganis et al. [18]. Intraobserver differences in the estimation of the P-wave parameters were not higher than 4%. The change in PWD (ΔPWD) was estimated as $PWD_{recovery} - PWD_{resting}$. The measurements of the PWD were performed with a 4-fold magnification of the tracings (100 mm/s, 40 mm/mV).

All the patients were scheduled by their attending cardiologist and underwent coronary angiography not later than 6 months after EST. Images were recorded in multiple projections for left and right coronary arteries using a Philips Allura FD10 Flat Panel System (Philips Healthcare, Nether-

Table 1. Demographic and clinical characteristics of the study population in respect of the coronary angiography result; means ± standard errors are shown.

Parameter	Coronary angiography		F; p value
	Non-coronary stenosis group (n = 156)	Coronary stenosis group (n = 109)	
Male	104 (67%)	73 (67%)	NS
Arterial hypertension	89 (57%)	54 (50%)	NS
Left ventricular hypertrophy	82 (53%)	51 (47%)	NS
Medical treatment:			
Beta-blockers	112 (72%)	77 (71%)	NS
ACE-inhibitors	102 (65%)	66 (61%)	NS
Statins	104 (67%)	73 (67%)	NS
Acetylsalicylic acid	105 (67%)	77 (71%)	NS
P2Y12 inhibitors	64 (41%)	40 (37%)	NS
Age	60 ± 0.85	63 ± 0.81	$F_{(1, 263)} = 6.023$, $p < 0.05$
Body mass index	29 ± 0.38	28 ± 0.41	NS
Ejection fraction [%]	56 ± 0.72	55 ± 1.01	NS
Max. ST-deviation [mV]	−0.08 ± 0.01	−0.09 ± 0.01	NS
Resting PWD_{II} [ms]	110 ± 1.02	113 ± 1.96	NS
Resting PWD_{V5} [ms]	107 ± 1.02	110 ± 1.82	NS
Recovery PWD_{II} [ms]	116 ± 1.29	121 ± 2.26	$F_{(1, 263)} = 4.055$, $p < 0.05$
Recovery PWD_{V5} [ms]	113 ± 1.29	119 ± 2.25	$F_{(1, 263)} = 4.369$, $p < 0.05$
ΔPWD_{II} [ms]	6.87 ± 1.13	8.15 ± 1.12	$F_{(1, 263)} = 3.432$, $p < 0.05$
ΔPWD_{V5} [ms]	6.51 ± 1.15	8.25 ± 1.53	$F_{(1, 263)} = 4.959$, $p < 0.05$

ACE — angiotensin converting enzyme; NS — non-significant; PWD — P-wave duration

lands). The interpretation of all the angiograms was made visually by experienced, certified (Polish Cardiac Society) interventional cardiologists. Significant coronary stenosis (coronary stenosis group) was defined as > 50% narrowing of vessel lumen.

Statistical analysis

All data were analyzed using Statistica Version 10 (Statsoft, Tulsa, United States of America). The differences were considered significant if p < 0.05. Continuous variables presented in text, tables and figures are means ± standard errors. Categorical variables are shown in absolute numbers and percentages. For the comparison of the qualitative data the χ^2 test was used. One-way analysis of variance was used to detect significant differences in changes of the measured parameters between the patients in the study groups (patients with ischemic EST results and non-ischemic EST results). The horizontal and vertical multiple pair-wise comparisons were made by means of the post hoc Tukey's test. Associations of P-wave measurements with clinical variables were assessed by the Pearson's correlation coefficient.

Results

Clinical and demographic characteristic of the study population

Baseline demographic and clinical characteristics of the study population in respect of the results of the coronary angiography are presented in Table 1. Coronary angiography revealed 156 patients with no significant coronary stenoses (non-coronary stenosis group) and 109 patients with the presence of significant coronary lesions (coronary stenosis group). In the coronary stenosis group, 31 (28.4%) patients had 1-vessel disease, 46 (42.2%) patients had 2-vessel disease, and 32 (29.4%) patients had

Table 2. Comparison of exercise stress test predictive factors in the overall study population and in respect of the presence of arterial hypertension in the medical history of patients and body mass index.

Predictive factor	Sensitivity (%): female/male	Specificity (%): female/male	PPP (%): female/male	NPP (%): female/male
Overall study population				
ST-segment deviation + other EST clinical and electrocardiographic abnormalities*	41 (51/37)	69 (63/72)	49 (49/47)	66 (66/61)
Recovery PWD in II and/or V_5 lead ≥ 120 ms	55 (56/48)	68 (51/70)	43 (44/47)	65 (66/60)
Recovery PWD in II and/or V_5 lead ≥ 120 ms + ST-segment deviation + other EST clinical and electrocardiographic abnormalities*	83 (83/82)	20 (26/18)	42 (40/44)	63 (63/62)
Increase in ΔPWD_{II} and/or ΔPWD_{V5}	44 (42/45)	62 (60/63)	44 (42/46)	66 (60/62)
Increase in ΔPWD_{II} and/or ΔPWD_{V5} + ST-segment deviation + other EST clinical and electrocardiographic abnormalities*	69 (71/67)	42 (40/42)	45 (45/45)	66 (68/65)
Predictive factor	**Sensitivity (%)**	**Specificity (%)**	**PPP (%)**	**NPP (%)**
Presence of arterial hypertension and abnormal body mass index				
Recovery PWD in II and/or V_5 lead ≥ 120 ms	49	59	40	67
Increase in ΔPWD_{II} and/or ΔPWD_{V5}	42	60	43	62
Population without arterial hypertension and abnormal body mass index				
Recovery PWD in II and/or V_5 lead ≥ 120 ms	63	91	83	77
Increase in ΔPWD_{II} and/or $\Delta PWDV_5$	64	95	85	81

*Exercise-induced chest pain, ventricular arrhythmia, hypotension, left bundle branch block; EST — exercise stress test; NPP — negative predictive power; PPP — positive predictive power; PWD — P-wave duration

3-vessel disease. In the study population, 92 EST tests were described as ischemic. Among ischemic EST, we found 18 cases with angina pectoris, 68 cases of horizontal or downsloping ST-segment depression, 7 cases of ST-segment in aVR, 11 cases of exercise-induced ventricular arrhythmia, 5 cases of exercise-induced hypotension, 3 cases of exercise-induced LBBB.

Analysis of the predictive value of EST parameters

There were no significant differences in resting PWD in both II and V_5 leads between both the coronary stenosis and non-coronary stenosis study population. The recovery PWD and the change in PWD (ΔPWD) were higher in patients with coronary stenosis in both II and V_5 leads (Table 1).

Sensitivity, specificity, positive predictive power (PPP), and negative predictive power (NPP) for each predictive parameter are presented in Table 2.

The sensitivity and specificity for the isolated ST-segment depression analysis were 31% (25% in female, 42% in male) and 76% (63% in female, 80% in male), respectively, and for ST-elevation in aVR 52% and 68%, respectively. However, elevation in aVR was described only in 7 cases of EST in men. The presence of a combination of ST-segment deviation with other EST-induced clinical and electrocardiographic abnormalities (such as exercise-induced chest pain, ventricular arrhythmia, hypotension, LBBB) increased the sensitivity of the test.

Abnormal recovery PWD in II and/or V_5 lead (≥ 120 ms) had 55% (52% in female, 66% in male) sensitivity and 68% specificity. The combination of abnormal recovery PWD in II and/or V_5 lead with ST-segment changes increased the test sensitivity in the diagnosis of significant CAD. Combined analysis of abnormal recovery PWD in II and/or V_5 lead with ST-segment depression analysis and

other EST-induced abnormalities had the highest sensitivity, but in this case a spectacular decrease in specificity was observed.

An increase in ΔPWD (positive value of ΔPWD) was characterized by 44% sensitivity (42% in female, 45% in male) and 62% specificity (60% in female, 63% in male). The combination of the increase in ΔPWD in II and/or V_5 leads with ST-segment depression and other EST-induced abnormalities (such as exercise-induced chest pain, ventricular arrhythmia, hypotension, LBBB) increased the sensitivity of the test in the detection of the presence of significant coronary stenoses, especially in females (71% in females and 67% in males).

The sensitivity and specificity of the abnormal recovery PWD in II and/or V_5 lead (≥ 120 ms) in the population with normal (non-ischemic) EST result was 20% and 76%, respectively (PPP 33%; NPP 62%). The sensitivity and specificity of the increase in ΔPWD in II and/or V_5 leads in the population with normal (non-ischemic) EST result was 67% and 13%, respectively (PPP 10%; NPP 71%).

Analysis of the predictive value of ΔPWD in II and/or V_5 and the extent of CAD

An analysis of the predictive value of PWD_{II}, PWD_{V5} with reference to the extent of CAD revealed higher sensitivity and specificity of the increase in ΔPWD in II and/or V_5 for left CAD: 69% and 47%, respectively (PPP 79%, NPP 56%). The sensitivity and specificity of the increase in ΔPWD in II and/or V_5 for the right coronary artery was 35% and 56%, respectively (PPP 37%, NPP 57%).

The sensitivity and specificity of abnormal recovery PWD in II and/or V_5 for the left coronary artery was 39% and 65%, respectively (PPP 45%, NPP 64%), and for the right coronary artery 31% and 67%, respectively (PPP 44%, NPP 60%).

The sensitivity and specificity of the increase ΔPWD in II and/or V_5 for 1-vessel CAD was 31% and 66% (PPP 29%, NPP 67%), respectively; for 2-vessel CAD 47% and 63% (PPP 49%, NPP 59%), respectively, and for 3-vessel CAD 70% and 50% (PPP 65%, NPP 58%), respectively.

Analysis of resting and recovery PWD — correlation with BMI, the presence of arterial hypertension and LV hypertrophy

The majority of the study population had abnormal BMI (BMI ≥ 25 kg/m^2, n = 218; p < 0.001) and the medical history of arterial hypertension (n = 144; p < 0.001). The dispersion of increased BMI and arterial hypertension were similar in all the study groups (Table 1). An analysis of the results in

the study subgroups revealed a positive correlation between BMI and resting PWD_{II} and PWD_{V5} values prior to the EST (r = 0.266, p < 0.01; r = 0.251, p < 0.05, respectively) (Fig. 1). There was a correlation between the presence of arterial hypertension in the medical history of the patients and PWD (Fig. 2). In hypertensive patients, the resting PWD_{II} was higher (115 $\pm$ 1.65 ms) in comparison with non-hypertensive patients (106 $\pm$ 1.65 ms; p < 0.001). EST increased PWD_{II} and PWD_{V5} in both hypertensive and non-hypertensive patients. In hypertensive patients, recovery PWD_{II} was higher (122 $\pm$ 1.70 ms) in comparison with non-hypertensive patients (113 $\pm$ 1.67 ms; p < 0.001). Also, a significant difference in the prolongation of recovery PWD between hypertensive (119 $\pm$ $\pm$ 1.71 ms) and non-hypertensive patients (110 $\pm$ $\pm$ 1.73 ms; p < 0.01) was observed in lead V_5. There were no differences in respect of the presence of arterial hypertension in ΔPWD in lead II. ΔPWD_{V5} was higher in hypertensive patients (7.49 $\pm$ $\pm$ 1.30 ms vs. 5.16 $\pm$ 1.14 ms; p < 0.05).
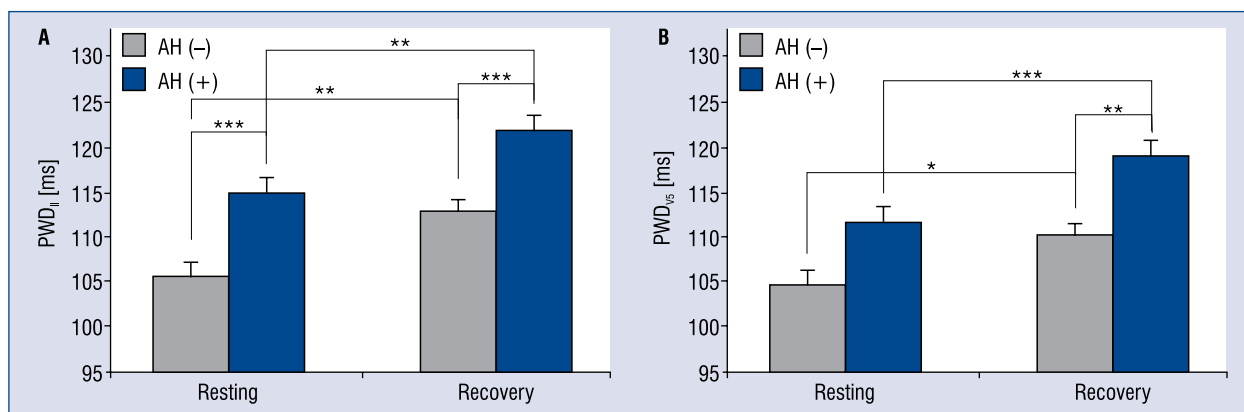
The presence of abnormal BMI and arterial hypertension influenced also the prognostic value of prolonged recovery PWD and the increase in ΔPWD in leads II and/or V_5. In the population with arterial hypertension and abnormal BMI, sensitivity and specificity of abnormally prolonged recovery PWD (≥ 120 ms) in leads II and/or V_5 was 49% and 59%, respectively. In the population without arterial hypertension and with normal BMI, prolonged recovery PWD (≥ 120 ms) during EST was described with 63% sensitivity and 91% specificity and had 83% PPP and 77% NPP, respectively. In the group of patients with both arterial hypertension and abnormal BMI, sensitivity and specificity of increased ΔPWD in leads II and/ or V_5 was 42% and 60%, respectively. In the study population without arterial hypertension and with normal BMI, sensitivity of increase in ΔPWD in leads II and/or V_5 was 64% with specificity up to 95% (PPP 85% and NPP 81%) (Table 2).

Discussion

The results of the study: 1) show low sensitivity of significant coronary occlusions identification by an analysis of isolated ST-segment deviation during EST; 2) indicate that the addition of an analysis of the increase in ΔPWD or prolonged PWD (≥ 120 ms) in leads II and/or V_5 to ST--segment changes and other electrocardiographic and clinical abnormalities observed during exercise stress tests (such as exercise-induced chest
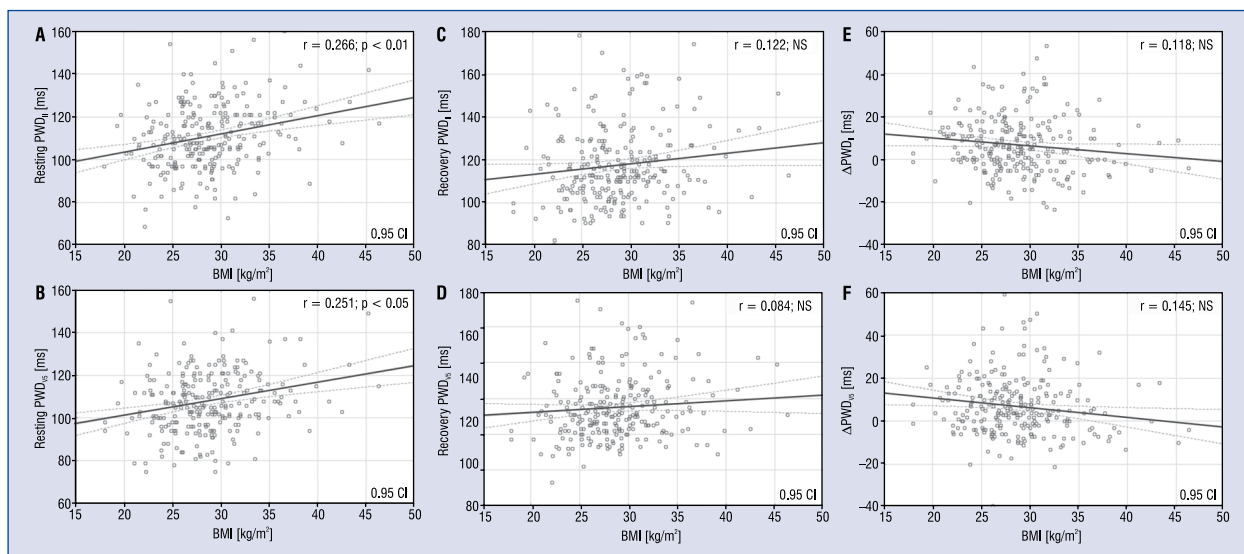
Figure 1. Univariate correlation (Pearson correlation) between body mass index (BMI) and resting PWD$_{II}$, PWD$_{V5}$ (**A, B**), recovery PWD$_{II}$, PWD$_{V5}$ (**C, D**), ΔPWD$_{II}$ and ΔPWD$_{V5}$ (**E, F**); PWD — P-wave duration; NS — non-significant.

Figure 2. The relation between the presence of arterial hypertension (AH) in the medical history of patients and resting (**A**) PWD$_{II}$ and PWD$_{V5}$ and recovery (**B**) PWD$_{II}$ and PWD$_{V5}$ values; means ± standard errors are shown; PWD — P-wave duration; *p < 0.05; **p < 0.01; ***p < 0.001.

pain, ventricular arrhythmia, hypotension, LBBB) increases sensitivity of the exercise stress test in the detection of significant coronary occlusions; 3) show higher sensitivity and specificity of the increase in ΔPWD in leads II and/or V$_5$ for left CAD and 3-vessel CAD. The present study, for the first time, provides evidence for the negative influence of the presence of arterial hypertension and, to a lesser extent, of the presence of abnormal BMI on the predictive value of P-wave changes during EST.

Results obtained in the present observation are consistent with the results of the study by Maganis et al. [18], where a combination of ΔPWD$_{V5}$

with ST-segment deviation increased sensitivity of EST in identification of myocardial ischemia from 34% (for ST-segment based evaluation of EST) to 79%. Maganis et al. [18] calculated that ΔPWD ≥ 20 ms correlated with myocardial ischemia, whereas in our study ΔPWD ≥ 20 ms was described in none of the cases of angiographically documented substantial coronary atherosclerosis. Moreover, most of the population of our study with angiographically documented significant coronary lesions had 2- or 3-vessel disease. According to the methodological postulates used in the present study, sensitivity of EST increased from 31% (ST-segment based

interpretation of EST) to 69%. Maganis et al. [18] evaluated the presence of ischemia in stress single-photon emission computed tomography (SPECT), while we related EST interpretation to coronary angiography results. The value of prolonged P-wave with EST in patients, who underwent coronary angiography, was also discussed by Myrianthefs et al. [15]. Nevertheless, the group of patients with significant CAD in this study was relatively small, the control group included some healthy volunteers and the incidence of comorbidities, such as arterial hypertension and obesity were not analyzed. Therefore, it is possible that higher intergroup difference in PWD could result from heterogeneity of the study groups. In our study, all groups were homogenous, so the obtained results were not affected by comorbidities other than significant CAD. Despite the high sensitivity (with dramatic decrease in specificity) of the combination of prolonged (≥ 120 ms) recovery PWD with other EST diagnostic criteria, we would rather advise ΔPWD analysis in the interpretation of EST. Moreover, in our observations, we noticed many cases of patients with abnormal resting PWD, who had decreased PWD on EST, but recovery PWD still remained abnormal.

In the present study, we also confirm the uncertain value of EST evaluation by isolated ST-segment deviations. Low sensitivity of ST-segment depression in V_4–V_6 has been described before [19, 20]. ST-segment deviations were found to have limited predictive value in CAD in women [21, 22].

Recent observations confirm the hypothesis that increased LV filling pressure (due to myocardial ischemia/damage, the presence of arterial hypertension, increased blood volume in the case of overweight/obesity) affects P-wave morphology in resting electrocardiography [8–10]. In our study, we found higher prognostic value of the increase in ΔPWD in leads II and/or V_5 for detection of left coronary artery stenosis (vs. right coronary artery). Moreover, the sensitivity and specificity of PWD in both II and V_5 increased with the number of coronary artery stenoses and was the highest for 3-vessel CAD. In the context of these results, we may support earlier hypotheses that PWD changes correlate with the severity of CAD [13] and with a rise in the LV filling pressure, as a result of myocardial ischemia [23]. In the classical model of myocardial ischemia cascade, angina symptoms are preceded by depolarization and repolarization changes on the electrocardiogram, which in turn are preceded by LV diastolic dysfunction from myocardial ischemia [24]. LV diastolic dysfunction

results in the increase in the LV filling pressure, which subsequently may increase left atrial pressure and/or diameter [25].

In the population of our study, the presence of overweight and obesity was similar in both groups. It should be noted, though, that in the present investigation, an increase in BMI also correlated with resting but did not affect recovery PWD.

In our study, we found a correlation between the presence of arterial hypertension in the medical history of patients and both the resting and recovery PWD. Dagli et al. [25] reported that resting PWD may be a good indicator for heart remodeling in hypertension as there is a correlation between high blood pressure, LV hypertrophy, diastolic dysfunction and increased volume of the left atrium. It was reported that P-wave morphology changes may result from left or right atrial hypertrophy and/or dilatation [26]. It is well known that physical exercise results in volume overload of both atria and ventricles. We expected that increased blood volume during exercise would change the sensitivity of P-wave changes in the diagnosis of CAD in the population of patients with arterial hypertension-related atrial volume or intra-atrial pressure changes. Regardless of the presence of hypertension, changes of PWD with EST still remain a good indicator of significant CAD.

Limitations of the study

Our study has some limitations. During the acquisition of the data from EST, both observers were blinded to the result of the test. That is the reason for the small sample of ischemic EST. However, it should be noted that all the patients underwent stress test during hospitalization. Most of the tests were submaximal due to treatment with beta-blockers and the general condition of the inpatients. The observers were not involved in the process of qualification neither for EST nor for coronary angiography. Also, both EST and coronary angiography were provided from 2009 to 2011, before the publication of the current guidelines on the management of stable CAD.

Conclusions

In conclusion, an analysis of the changes of PWD should be introduced into standard interpretation of exercise stress test as it has been shown to be a useful electrocardiographic tool in the prognosis of significant coronary lesions due to the increase of sensitivity in detection of the disease. Our study also brought out the problem of low

sensitivity of ST-segment deviation-based EST--interpretation. According to the growing number of data suggesting the prognostic and diagnostic utility of PWD and the variable prognostic value of ST-segment deviations during EST in the diagnosis of CAD, novel specific criteria for clinical application in EST should be discussed and established.

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