ORIGINAL ARTICLE

TWARMI pilot trial: The value and optimal criteria of microvolt T-wave alternans in the diagnosis of reversible myocardial ischemia in patients without structural cardiac disease

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Abstract

Aims: Microvolt T-wave alternans (MTWA) testing is a beat-to-beat fluctuation in the amplitude of T wave. We investigated whether: (a) MTWA can be new non-invasive tool for detection of reversible ischemia in patients with suspected CAD without structural heart disease, (b) MTWA can detect ischemia earlier and with greater test accuracy compared with exercise ECG ST-segment testing, and (c) threshold value of MTWA and heart rate at which the alternans is estimated can be different compared to standard values.

Methods: A total of 101 patients with suspected stable coronary disease, but without structural heart disease, were included. Echocardiography, exercise ECG test, MTWA with classical and modified threshold alternans values, and coronary angiography were performed.

Results: About 33.3% patients had a false-positive result on exercise ECG test. The sensitivity of exercise ECG ST-segment test in the detection of coronary artery disease was 97.8%, and the specificity was 42.5% (DOR 33.89). In a group of angiographically positive patients, standard MTWA accurately identified 60% of patients, while 40% had a false-negative result. About 91.8% patients with negative angiography result were accurately identified with 8.2% false positives. The sensitivity of MTWA was 59.61% and specificity 91.83%. Best ratio of sensitivity and specificity (86.53% and 95.91%, DOR 151.06) had modified criteria for positive MTWA (MTWA >1.5 μ V at heart rate 115–125/min).

Conclusions: This study showed that MTWA can be the new non-invasive tool for the detection of reversible ischemia in patients with suspected CAD without structural heart disease. Also, MTWA can detect ischemia earlier and with greater accuracy compared with exercise ECG testing.

KEYWORDS

coronary artery disease, exercise ECG test, microvolt T-wave alternans

1 | INTRODUCTION

Stable coronary artery disease (CAD) is characterized by episodes of reversible myocardial demand/supply mismatch related to ischemia (hypoxia). There are many non-invasive cardiac investigation tools that can be used to support the diagnosis of stable CAD (Genders et al., 2011). Exercise electrocardiogram (ECG) test is completely non-invasive, broadly available, and low-cost test. It performs well at intermediate pretest probability between 15%–65%, but sensitivity is lower (45%–50%) compared to imaging techniques (Fihn et al., 2012). Test has limited or no diagnostic value in the presence of left bundle branch block (LBBB), Wolff–Parkinson–White (WPW) syndrome, paced rhythm, ECG signs of LVH, electrolyte imbalance, intraventricular conduction abnormalities, and use of digitalis etc (Pradhan, Chaudhary, & Donato, 2012). Also test may be inconclusive when 85% of maximum heart rate is not achieved (Montalescot & Sechtem, 2013). Microvolt T-wave alternans (MTWA) is a beat-to-beat fluctuation in the amplitude of T wave at a microvolt level. The amount of variation is small, on the order of microvolt, so sensitive digital signal processing techniques are required to detect it (Haghjoo, Arya, & Sadr-Ameli, 2006). Several lines of evidence suggest that electromechanical alternans is linked to alterations in cellular Ca^{2+} homeostasis (Pastore, Girouard, Laurita, Akar, & Rosenbaum, 2007). Calcium homeostasis is not only important for excitation-contraction coupling, but it also significantly influences the action potential (AP) profile and duration (APD) (Choi & Salama, 2012). It has been suggested that altered restitution of the calcium transient, a multistep process involving Ca^{2+} uptake into the sarcoplasmic reticulum (SR), redistribution in the SR, and release through the ryanodine receptor, may underlie alternans. The profound cellular metabolic disturbances in ischemic hearts almost certainly play a role in the induction of mechanical and electrical alternans (Shimizu & Antzelevitch, 1999). In support of a theory that links the occurrence of cardiac alternans to decreased energy availability in the ischemic cell, it was suggested that the occurrence of alternans may be associated with the inhibition of adenosine triphosphate (ATP) production, thus affecting excitation-contraction coupling, perhaps on an every-other-beat basis. Prolongation of repolarization favors re-entry when the prolongation is heterogeneous, and dispersion of refractoriness is significantly enhanced (Chinushi, Restivo, Caref, & El-Sherif, 1998). This dispersion of refractoriness hypothesis states that intrinsic dispersion of ventricular refractoriness prevents myocytes with the longest recovery times from depolarizing, or from depolarizing completely, every other cycle, resulting in a 2:1 behavior on the surface ECG.

T-wave alternans testing has been studied as a non-invasive predictor of potentially lethal ventricular arrhythmias of diverse patient populations with structural heart disease, but there is just few clinical study that examines value of MTWA for detection of ischemia. According to suggested mechanism of MTWA formation, we investigated whether: (a) MTWA can be the new non-invasive tool for the detection of reversible ischemia in patients with suspected CAD without structural heart disease, (b) MTWA can detect ischemia earlier and with greater sensitivity and specificity compared

with exercise ST-segment change testing, and (c) threshold value of MTWA and heart rate at which the alternans is estimated can be different compared to values in prediction of lethal arrhythmias.

2 | METHODS

A total of 101 consecutive patients with suspected stable coronary disease, but without previous structural heart disease, were included. Study was multicentric, and it was made in three international centers (University Clinic for cardiovascular diseases, Clinical Hospital Centre Zagreb; Department of Cardiology and Electrotherapy, Medical University of Gdansk, Poland, and Cardiology Department, S. Cuore Hospital, Verona VR, Italy). Recruitment of patients lasted from 2015 to 2017. Study complies with the Declaration of Helsinki and was approved by all the hospital committees, and all patients gave informed consent. Patients mostly complained on retrosternal pain or dyspnea in exercise. Structural heart disease was excluded by medical history, ECG, and echocardiography (normal left ventricular diastolic diameter, normal global and regional systolic function, no important hypertrophy, or valvular disease; GE Vivid 7, General Electric Company, New York, NY, USA). After initial checking of including criteria, blood tests (blood count, electrolytes, lipidogram, creatinine, blood gases, and troponine), and exercise ST-segment change test by treadmill were performed. Next day MTWA was analyzed, and lastly in all patients quantitative coronary angiography as a “gold standard” for CAD confirmation was performed. In the same procedure, percutaneous coronary intervention and stenting was made as needed. Operator was blinded to the results of MTWA and ECG stress test. Exercise ST-segment change test was made according to standard Bruce protocol (Fletcher et al., 2016; Quinton Q-Stress TM55; Cardiac Science, Germany). The reversible ischemia was confirmed if, in exercise or immediately after exercise, ST segment (J point) was depressed at least 1.0 mm, depression persisted at least 0.08 s after J point in at least three consecutive QRS-ST-T complexes and in at least one ECG lead (Fletcher et al., 2016). We used standard 12 leads ECG system. We performed test until at least submaximal expected workload. MTWA was analyzed by spectral method according to suggested protocol (HearTwave II; Cambridge Heart, Tewksbury, MA, USA; Armoundas et al., 2003; Armoundas, Rosenbaum, Ruskin, & Cohen, 2004). We used cycloergometer because artifacts are seldom compared to treadmill equipment. After adequate preparation of the skin, placing the Micro-V alternans sensors, standard 12 leads ECG sensors, and checking the adequacy of all signals, examinee starts cycling (Bloomfield, Hohnloser, & Cohen, 2009). Initial load of 15 W was individually changed in order to achieve heart rate 100–110/min when T-wave alternans measuring starts. Examinee retains this heart rate for 2.5 min, and after that increase load to increase heart rate to 110–115/min for next 1.5 min. After the test was performed according to the standard protocol, the load is increased in order to raise the heart rate to 115–125/min for at least 1.5 min. Analytic spectral method software automatically measures MTWA, processes the data, and interpretes the results.

Along with graphical display automatically conclusion can be positive alternans, negative alternans, and indeterminate result. In the case of the third option, we repeated the test and if result was again indeterminate, according to manufacturer suggestion, these patients were considered as positive result until definitive diagnosis (Chan, Bartone, Booth, Kereiakes, & Chow, 2007). Software interprets result as positive if MTWA is at least 1.9 μ V during at least 1.0 min in any vector (X, Y, Z), or two precordial ECG leads (Verrier et al., 2007). In addition to these automatic interpretations of MTWA with criteria that apply to sudden cardiac death, from the graphical display we manually measured the size and duration of T-wave alternans also at a higher heart rate. We used digital zoom and cardio caliper for precise measuring. Along to the standard criteria of automatic interpretation, we analyzed the results with respect to the threshold level of MTWA of at least 1.5 μ V and with heart rate of 115–125/min. CAD was significant if there was more than 50% stenosis of at least one of the main coronary arteries (LAD, Cx, and RCA). Coronary angiography was performed on the "Axiom Artis, Siemens, USA" equipment. Statistical analysis continuous variables are shown as mean and standard deviation while categorical variables are expressed as absolute numbers and percentages. Categorical variables were tested with χ^2 or Fisher's exact test while for continuous variables we used independent T test or Mann–Whitney U-test depending on types of distribution. For distribution testing, we used Kolmogorov–Smirnov test for variable normality. Statistical significance for all tests was expressed as two-tailed $p < 0.05$ value. Statistical analysis was performed with SPSS 15.0 statistical package. We have calculated test accuracy and DOR (diagnostic odds ratio). It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive and if the subject does not have the disease. The rationale for the diagnostic odds ratio is that it is a single indicator of test performance but which is independent of prevalence. Test accuracy refers to the percentage of patients correctly classified by the test. This percentage depends on the prevalence of the target disorder in the study group whenever sensitivity and specificity are not equal, and it weights false-positive and false-negative findings equally.

3 | RESULTS

Baseline clinical characteristics of the study population are shown in Table 1. All values are measured in SI units. Except that men had significantly higher hemoglobin, in other parameters there were no differences according to sex. The left ventricular diastolic diameter was 5.18 (0.52) cm (M 5.32 [0.39], F 4.93 [0.63]) and ejection fraction 61.4 (4.5) % (M 60.9 [3.4], F 62.2 [5.9]). Coronary angiography was positive in 52 (51.4%) examinees (M 46, F 6, while 49 (48.5%) patients (23 males and 26 females) had no significant changes in coronary vessels. In the group with CAD, 48% patients had significant disease of the LAD with a mean stenosis 89.1 (17.7)%, 34% subjects had stenosis of the RCA with an average value of 81.6 (12.6)%, and 17% patients had stenosis of the Cx with an average value of 76.6 (10.3)%. Although

TABLE 1 Baseline clinical characteristics of the study population

	Males	Females	Total
Number	69 (68.3%)	32 (31.7%)	101
Age	61 (11.9)	62 (10.6)	61 (11.3)
Family history of CAD	14 (20.3%)	2 (6.2%)	16 (15.8%)
Smoking	20 (28.9%)	16 (0.5%)	36 (35.6%)
Diabetes	6 (8.6%)	3 (9.3%)	9 (8.9%)
Hemoglobin	144.4 (10.9)	135.9 (6.1)	141.3 (10.2)
Potassium	4.17 (0.26)	4.39 (0.33)	4.25 (0.30)
Calcium	2.42 (0.17)	2.36 (0.17)	2.40 (0.17)
Creatinine	102.2 (16.7)	92.1 (25.2)	98.6 (20.5)
Cholesterol	5.45 (1.02)	5.41 (0.73)	5.44 (0.92)
LDL	3.53 (0.82)	3.17 (0.66)	3.40 (0.78)
HDL	1.17 (0.16)	1.58 (0.56)	1.32 (0.40)
Triglyceride	1.60 (0.71)	1.43 (0.67)	1.54 (0.69)
Troponine	0.00	0.00	0.00
Echo LVDD	5.32 cm	4.93 cm	~5.18 cm
EF	60.9%	62.2%	61.4%
Positive coronarography	46	6	52
Negative coronarography	23	26	49

the average values of stenosis in the male population were higher (80%–91%) comparing to female population (70%–79%), differences were not statistically significant. Considering the number of vessels with significant stenosis (46.2%) patients had a stenosis of one, while (53.8%) patients had a double vessel stenosis. Table 2.

About 13.8% of all examinees had inadequate test due to not achieving adequate frequency or significant nuisance and artifacts in ECG which prevented an objective assessment of ischemia. Females achieved significantly lower frequency compared with males. About 33.3% of men and 23.1% of women were positive in the anterior leads, while 66.7% of men and 78.9% of women had a positive finding in the inferior leads. However these differences were not found to be statistically significant Table 3. In the group with no significant CAD, 26.4% had a false-positive result on ECG exercise ST-segment

TABLE 2 Results of exercise ECG ST-segment change testing

Test result	Males	Females	Total
Positive	51 (73.9%)	18 (56.2%)	69 (68.3%)
Negative	10 (14.5%)	8 (25%)	18 (17.8%)
Inadequate	8 (11.6%)	6 (18.8%)	14 (13.7%)
Max. heart rate	148.6 (13.1)	139.9 (11.7)*	145.4 (13.2)
METS	7.28 (1.75)	6.52 (1.24)	7.00 (1.60)

* $p = 0.026$.

change test. On the other hand, in the group with significant CAD, just one of the patients had false-negative finding of exercise ST-segment change test. Correlation of coronary angiography results and the results of exercise ST-segment change test were statistically significant ($p = 0.000$). About 13.8% of examinees who had inadequate stress test result in this case were not taken into consideration. In male patients without significant CAD, 15.9% of patients had a false-positive result on exercise ST-segment change test while in the male group with significant disease there were no false-negative exercise ST-segment test results. Relation of the findings on coronary angiography and exercise ST-segment change test was

TABLE 3 Correlation between results of coronary angiography and exercise ECG ST segment change test (14 patients were excluded because test was inconclusive—pacemaker presence, left bundle branch block, not achieved submaximal frequency)

Coronary angiography	Exercise ECG test		
	Positive	Negative	Total
Positive			
M	40	1	47
F	6	0	
Negative			
M	11	9	40
F	12	8	
Total	69	18	87

Males $p = 0.001$; females $p = 0.03$.

statistically significant ($p = 0.000$). In female patients without significant CAD, 37.5% had a false-positive exercise ST-segment change test while in the group with significant CAD no one had false-negative exercise test result. The sensitivity of exercise ST-segment change test in the detection of CAD in our study was 97.8%, and the specificity was 42.5%. In accordance with a reduced specificity of the female population, positive predictive value (PPV) is significantly lower in women (33%) compared to the male population where PPV was 78.4% Table 4. Positive MTWA had 15 patients (14.8%), negative findings 66 patients (65.3%), while the finding was indeterminate in 20 patients (19.8%). A total of 45 MTWA-negative patients had no significant CAD while 21 patients had a false-negative result. When, in accordance with the manufacturer's recommendations and literature, all inconclusive findings of MTWA were included in coronary angiography positive group (non-negative group), then in a group of angiographically positive patients MTWA accurately identified 59.6% of patients, while 40% had a false-negative result. On the other hand, 91.8% angiographically negative patients were accurately identified with 8.1% false positives. Correlation of MTWA and coronary angiography was highly significant ($p = 0.000$). At higher heart rate (115–125/min) with a MTWA value of $>1.9 \mu\text{V}$, there were significantly less false-negative results of MTWA (17 patients 26.1%) compared to the standard automatic interpretation. If with a standard heart rate (105–115/min) we take value $>1.5 \mu\text{V}$ for positive MTWA, then with 97.9% correlation of negative findings, 15 patients (23.8%) had a false-negative result of MTWA. The best results were found when the lower limit for MTWA ($>1.5 \mu\text{V}$) was assessed at higher heart rate (115–125/min) (Table 5). In these criteria, 2 (4.2%)

TABLE 4 Correlation between results of coronary angiography and microvolt T-wave alternans

A) Automatic interpretation				
	T-wave alternans			
Coronary angiography	Positive	Negative	Indeterminate	Total
Positive	13	21	18	52
Negative	2	45	2	49
Total	15	66	20	101
(B) Automatic interpretation when indeterminate (borderline) results are included in positive group (non-negative group)				
	T-wave alternans			
Coronary angiography	Positive	Negative		Total
Positive				
M	29 (29%)	17 (17%)		46 (45.5%)
F	2 (2%)	4 (4%)		6 (6%)
Total	31 (31%)	21 (21%)		52 (51.5%)
Negative				
M	4 (4%)	19 (19%)		23 (23%)
F	0 (0%)	26 (25.5%)		26 (25.5%)
Total	4 (4%)	45 (44.5%)		49 (48.5%)

(A) $p = 0.00005$; males $p = 0.001$; females $p = \text{nonsignificant}$. (B) $p = 0.00000$; males $p = 0.002$; females $p = 0.03$.

TABLE 5 Correlation between results of coronary angiography and modified criteria of microvolt T-wave alternans (>1.5 μ V with heart rate 115–125/min)

Coronary angiography	T-wave alternans		
	Positive	Negative	Total
Positive			
M	41	5	46
F	4	2	6
Total	45	7	52
Negative			
M	2	21	23
F	0	26	26
Total	2	47	49

$p = 0.00$; males $p = 0.00$; females $p = 0.00$.

patients showed false-positive MTWA, but unlike other combination of criteria, only seven patients (12.9%) had a false-negative MTWA result. The sensitivity and specificity of the test in these criteria was 86.5% and 95.91%. For standard automatic interpretation in both population correlation was also highly significant (but with less significance in female population). In the male patients, sensitivity was 89.1% and specificity 91.3%. In the female patients, sensitivity was 100% and specificity of 92.8%. Correlation between findings of coronary angiography and modified criteria of MTWA was also significant ($p < 0.000$).

4 | DISCUSSION

The clinical picture of stable CAD is characterized by typical angina problems, meaning pain retrosternally induced by mental and physical effort, turning out in the cold, after eating etc. But no small part of patients have atypical picture as choking, shortness of breath, and arrhythmia, etc. These atypical presentations such as the name suggests are not specific for CAD. Thus, in this study, although all patients had clinical features suggestive of stable CAD, only 51.4% had significant CAD on coronary angiography. The percentage of patients with a clinical picture that indicates angina without objective findings of significant CAD was significantly higher in female subjects. Stress ECG test can be considered as a “screening” method for invasive evaluation of patients with suspected CAD. Stress ECG still has relatively low sensitivity and specificity. Sensitivity in published analyses quite varied (from 23% to 100%, average 68%) while the specificity ranged between 17% and 100% with a mean of 77% (Fletcher et al., 2016). In our group, the sensitivity was 97.8% and specificity 42.5%, which corresponds to the previous literature. Women had slightly lower specificity compared to men (40:45%) which means that in the female population was significantly higher number of false positives. In accordance with a reduced specificity of the female population PPV was also significantly lower (33%) than in the male population, where it was 78.4%. PPV is strongly dependent on the prevalence

of the disease, that is, the probability of occurrence of the disease in the study population. Our population consisted of subjects with an average age of 61 (± 10) years where women with atypical angina had only a low probability of CAD. This would then explain the lower specificity and PPV compared to males, as is known in the literature. An additional reason for a false-positive stress ECG may be a hormonal influence on ion channels (Zheng, Shi, You, Ji, & Roesch, 2005). ST segment is the only electrical changes which indirectly indicates a potential ischemia. Reasons for false-positive stress ECG continue to be multiple concomitant administrations of drugs such as digitalis, left ventricular hypertrophy (LVH), pre-excitation, and LBBB etc. Really positive stress ECG finding with the negative result of coronary angiography is characteristic of X syndrome, that is, changes in the small blood vessels. These are the reasons why the value of the stress ECG in the diagnosis of CAD, particularly in patients that had no known CAD (not registered as proven coronary patients), is only moderate. Test accuracy was 72.41%. T-wave alternans could be useful parameter in predicting the risk of sudden death in patients with significant structural heart disease. In this indication, its value is in the high negative predictive value (NPV) (Kraaier, Olimulder, van Dessel, Wilde, & Scholten, 2014; Merchant et al., 2015). Patients with negative findings have a low probability of occurrence of malignant arrhythmias. PPV was relatively low. Patients in these studies had significant structural disease, respectively, potential arrhythmogenic substrate. Because the MTWA is interpreted as a consequence of calcium traffic disturbance, the question is whether the ischemia-induced disruption of the channels is of such intensity that may cause MTWA in patients who have no structural heart disease and that outside ischemia practically have no functional cardiac disorder. Hypoxia leads to diminished intracellular concentrations of ATP (adenosin triphosphate). Consequently, there is decreased activity of ATP-dependent transport systems. Na^+/K^+ -ATPase pump, one of the systems, normally transport K^+ into the cell and Na^+ out of the cell (Issa & Miller, 2012). Loss of pump activity induces increase in extracellular K^+ concentration and, in accordance with the Nernst equation, membrane depolarization (Oudit & Zipes, 2009). Depolarization inactivates fast Na^+ channels which decrease conduction velocity. Owing to the hypoxia, intracellular pH decreases. Efflux of H^+ from myocyte in exchange for Na^+ lead to greater $\text{Na}^+/\text{Ca}^{++}$ exchange across the cell membrane (Kapur, Wasserstrom, Kelly, Kadish, & Aistrup, 2016). Also lack of ATP decreases activity of sarco/endoplasmic reticulum Ca^{++} -ATPase (SERCA2a) (Bodi & Mikala, 2005). Described processes lead to increased intracellular Ca^{++} concentration, longer duration of AP, disorder of myocardial relaxation, and later local systolic dysfunction.

As for the evidence of ischemia in exercise ECG testing it is necessary of achieving sufficient heart rate, there is the question of whether MTWA can show ischemia at lower heart rate comparing to exercise ST-segment change testing, that is, whether it is more sensitive and specific parameter for the detection of ischemia. There is one study (Figliozzi et al., 2016) that shows that MTWA is increased in patients with obstructive CAD and is reduced by coronary revascularization. Their results showed that MTWA with

standard criteria for positive test had 95% specificity and 82% PPV in obstructive CAD group. After PCI number of positive MTWA decreased. Results indicate that assessment of MTWA can be helpful in identifying which patients with suspected CAD are likely to show obstructive CAD on angiography. Our study shows similar results. The sensitivity of T-wave alternans was 59.61% and specificity 91.8%. In the male population, sensitivity was 63% and specificity 82%. In the female group, the sensitivity was significantly lower (33%), but due to small number of positive findings, could not be objectively calculated. This difference could perhaps be explained by a higher proportion of women who have had a significant stenosis of the LCx compared to males where LCx stenosis was in only of patients. It is known that LCx stenosis less affects the positive findings of stress ECG test, so potentially lower zone of ischemia can also affect less positivity of T-wave alternans. In addition, a larger proportion of males, compared to females, had two coronary vessels with significant stenoses. Two significantly stenosed coronary vessels provide greater zone of ischemia and a greater possibility of a positive result, regardless of the type of test. The PPV of 88.5% for the entire group (87.8% for men and 88.5% for women) shows that practically almost every patient with a positive test had also significant CAD. This is significantly better than what we obtained for stress ECG test in the total population as well as considering gender. The average rate achieved on exercise ST-segment change testing was 145 (13) per minute while the MTWA was examined at the heart rate 110–115/min. This indicates that the MTWA can show ischemia at low load, that is, at lower heart rate, which means that, compared to ergometry, it is more sensitive in the early diagnosis of ischemia.

When alternans was estimated at heart rate higher than the standard recommendation, the results were not significantly changed. There were also no significant changes even when, we took lower MTWA value (1.5 V) for the positive test. This can be explained by the fact that when the result with standard criteria is inconclusive,

usually when the MTWA is present, but the value is lower than 1.9 μ V. That is reason for recommendation to do “non-negative” group of patients. The best ratio of sensitivity and specificity (86.5% and 95.9%) was found at higher frequencies (115–125/min) and when the criteria for a positive MTWA were lower (≥ 1.5 μ V). Test accuracy was 91.09%. This ratio was better, with significantly lower heart rate (115–125/min) compared with exercise ST-segment change test (with heart rate 145/min). By enlarging zone of ischemia with a little higher heart rate and lower threshold MTWA level, we increase sensitivity without important decrease in specificity. According to the studies of the risk of malignant arrhythmias in patients with structural heart disease, heart rate greater than 120/min were followed by a higher incidence of MTWA in the control group. As the aim of that studies was prediction of malignant arrhythmia where new coronary angiography was not systematically performed, there is possibility that some of patients had latent coronary ischemia causing positive MTWA with higher heart rate. It is interesting that in this study we did not obtained a significant correlation between stress ECG test and T-wave alternans in the total group nor with regard to gender ($p = 0.077$). This indicates that the T-wave alternans shows different electrical disturbance in the ischemic myocardium compared to the ST-segment change in stress ECG test. Correlation would perhaps be pointed on a larger number of patients. But for the evidence on the value of MTWA in the diagnosis of CAD it is not crucial, because statistical significance, the sensitivity and specificity even in this small group of subjects was high. Although sensitivity and PPV were slightly larger for ECG stress testing, there was large number of false-positive patients and consequently unnecessary need for invasive testing. MTWA with modified criteria testing did not have large number of false-positive and false-negative patients. When we calculate test accuracy (Glas, Lijmer, Prins, Bonsel, & Bossuyt, 2003) and DOR (diagnostic odd ratio) (Glas et al., 2003), modified criteria for positive MTWA (MTWA >1.5 μ V at heart rate 115–125/min) had greater accuracy (91.09%) and DOR (151.06) than ECG stress test

FIGURE 1 Correlation between different MTWA criteria and Stress ECG ST-segment change test

(accuracy 72.41%, DOR 33.89). Also, advantage of MTWA is that patients with LBBB and pacemaker can be tested, and test is positive with lower heart frequency than ECG stress test.

5 | CONCLUSIONS

This study proves that MTWA can be the new non-invasive tool for the detection of reversible ischemia in patients with suspected CAD without structural heart disease. The sensitivity of exercise ST-segment change test in the detection of CAD was 97.8%, and the specificity was 42.5% (PPV 66%, NPV 94%). Test accuracy was 72.41%. The sensitivity of MTWA was 59.6% and specificity 91.8%. The best ratio of sensitivity and specificity had modified MTWA criteria (MTWA >1.5 μ V at heart rate 115–125/min) (86.5% and 95.9%). PPV for modified MTWA criteria was 95.7% and NPV 87% (Figure 1). Test accuracy for modified MTWA criteria was 91.09% and DOR 151.06. MTWA can detect ischemia earlier and with greater test accuracy compared with exercise ST-segment change testing.

6 | STUDY LIMITATIONS

The study was conducted on a relatively small number of patients. However, since we demonstrated a high statistical significance we believe that the data for the total population and the male subgroup were clearly confirmed. Taking into consideration that the number of female respondents was relatively small, especially in the group with a positive coronary angiography, actual value of T-wave alternans in the female population should be tested at a much larger sample. Also, we have to mention that MTWA was calculated during bicycle ergometry to avoid artifacts while ST-segment was calculated during treadmill testing. Criteria of positive alternans with the best balance of sensitivity and specificity with respect to the amplitude of alternans and the target heart rate are set for prediction of sudden death in patients with structural heart disease. In our research, the best balance of sensitivity and specificity for diagnosis of reversible ischemia was with lower MTWA threshold and with higher heart rate. Therefore, the research can be seen as a pilot study and encouragement for large multicenter study with a view to a definitive confirmation of criteria and values of MTWA for the diagnosis of reversible ischemia in patients without structural heart disease and helpful diagnostic test for patients who cannot achieve necessary heart rate, patients with LBBB or pacemaker, and rule out unnecessary invasive testing.

CONFLICT OF INTEREST

None declared.

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