Seminars in Cardiovascular Medicine, 2015; 21:9–15 e-ISSN 1822-7767

Original paper

Diagnostic value of electrocardiogram stress testing in patients with metabolic syndrome

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Received 2 March 2015; accepted 14 April 2015

Summary

Objectives: The aim of this study was to assess the diagnostic value of exercise stress testing to detect coronary heart disease (CHD) in the group of patients with metabolic syndrome.

Design and methods: 2803 patients without prior diagnosis of CHD and identified metabolic syndrome were investigated. Subjects underwent electrocardiogram (ECG) stress testing and, depending on the results, coronary angiography and/or coronary computed tomography angiography to detect hemodynamically significant stenosis. CHD was confirmed, if lumen narrowing $\geq$ 50% of coronary arteries was found.

Results: Exercise stress testing was interpreted as positive in 12% patients (71.7% women and 28.3% men). CHD was diagnosed in 45 patients (1.6%), 23 of them had positive exercise stress testing. ECG stress testing was more frequently positive in patients, who had typical/atypical anginal chest pain, dyspnea and/or non-anginal chest pain, in comparison to asymptomatic patients (16.6% vs 8.9%, $p < 0.001$). CHD was more often diagnosed in symptomatic patients compared to patients with no symptoms (6.1% vs 0.7%, $p < 0.001$, women 5.3% vs 0.6%, $p < 0.001$, men respectively 8% vs 0.8%, $p < 0.001$).

Conclusions: Diagnostic value of exercise stress testing for detecting CHD is limited in population with metabolic syndrome. CHD was more prevalent in patients with chest pain or dyspnea than in asymptomatic patients.

Seminars in Cardiovascular Medicine 2015; 21:9–15

Keywords: coronary heart disease, electrocardiogram stress testing, metabolic syndrome

Introduction

Coronary heart disease (CHD) is a chronic illness with an increasing incidence in the general population assuming epidemic proportions [1]. According to the World Health Organization (WHO), there were 7.4 million deaths due to CHD across the world in 2012 [2]. Despite efforts to reduce CHD morbidity and mortality, the prevalence of metabolic syndrome (MS), a risk factor for CHD, has been increasing in recent years as well [3]. Metabolic syndrome is a cluster of obesity, impaired glucose tolerance, high blood pressure and dyslipidemia, which is associated with a 2-fold increase in the risk of developing CHD [4]. Consequently, early detection of CHD is of high importance in preventing future cardiovascular complications in patients with MS.

Patients identified as having an increased risk of developing CHD usually undergo an exercise stress electrocardiogram (ECG). Despite well-known limitations of ECG stress testing, such as low sensitivity and specificity [5,6], high rate of false-positive results [7], this method is still widely used in screening and assisting the diagnosis of CHD [8,9]. ECG stress test is a non-invasive, inexpensive tool, which is also beneficial for stratifying prognosis in patients with suspected CHD [10]. Beyond ST-segment depression and chest pain occurrence during exercise [6], ECG stress test provides other valuable diagnostic informa-

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tion, including exercise capacity, chronotropic and blood pressure response, heart rate recovery and the Duke Treadmill Score [9]. Moreover, negative ECG stress test results allow patients to avoid coronary angiography [11].

Although coronary angiography is a "gold standard" test for patients, who have chest pain and are at high CHD risk [12], it is an invasive method [8]. Furthermore, coronary angiography, performed because of straightforward angina symptoms, may not always detect more hemodynamically significant stenosis [13].

It is important to note that many patients with prognostically significant CHD are asymptomatic [14]. This finding encouraged to investigate, whether a routine cardiac screening for CHD in asymptomatic patients is beneficial. Recently, it was revealed that screening with stress testing in asymptomatic, low-risk adults does not improve patient outcomes and may also lead to unnecessary tests [15]. However, there is limited information on how screening with ECG stress test improves CHD outcomes in subjects with MS.

The aim of this study was to evaluate exercise stress testing diagnostic value to detect CHD in patients with MS.

Design and methods

Study population

The study was retrospectively carried among 2803 patients – 1666 women at the age of 50–65 years and 1137 men at the age of 40–55 years with MS and without the presence of cardiovascular disease (CVD). All patients were recruited from the Lithuanian High Cardiovascular Risk (LitHiR) primary prevention programme between 2011–2013 years at the Vilnius University Hospital Santariškių Klinikos [16]. Patients' demographic and clinical data, symptoms were retrospectively collected from their medical records. All patients were assigned to two groups: (1) patients with symptoms, such as dyspnea, non-anginal chest pain, typical angina and atypical anginal chest pain and (2) asymptomatic patients.

Exclusion criteria were: diagnosed CHD, neoplasms, kidney or liver failure, permanent arrhythmias, drug-resistant tuberculosis, acute rheumatic fever or rheumatic disease (acute phase), pulmonary arterial hypertension (greater than grade 2), decompensate heart disease, lymphatic vessels and lymph node diseases with expressed lymphostasis, advanced stage of mental illness. Approval was obtained from the Lithuanian Bioethics Committee.

ECG stress testing

In 2803 subjects ECG stress testing was performed – patients had to pedal a stationary exercise bicycle while the load was increased from 50 W by 50 W every 3 minutes until subjects reached their submaximal workload (it is calculated by formula: $(220 - \text{age}) \times 0.8$ for men and $(210 - \text{age}) \times 0.8$ for women). During this test ECG was monitored for any signs of ischemia, heart rate, blood pressure and symptoms (angina/dyspnea) were recorded at regular intervals throughout the exercise test.

Criteria to stop ECG stress testing included patient request, specific ECG changes (ST-segment shifts, arrhythmias – third degree AV block, atrial fibrillation, ventricular or supraventricular tachycardia), moderate to severe dyspnea or angina and abnormal blood pressure responses [17]. Ischemia was identified based on the ECG criteria: horizontal or downsloping ST-segment elevation or depression ≥ 1 mm [18]. ST segment depression or elevation was measured relative to the isoelectric baseline (between the T and P waves) at a point 60–80 ms after the J point [19]. According to the level of ST-segment depression, results of ECG exercise testing were divided into three groups: positive (ST depression ≥ 1 mm in at least two leads), negative (ST depression was not observed) and uncertain (0–1 mm ST depression). If sub-maximal workload was not reached, ECG stress testing was considered as non-informative.

After ECG exercise testing, depending on the results, coronary angiography or coronary computed tomography angiography (CCTA) were performed in order to detect coronary heart disease (CHD). It was considered if coronary angiography or CCTA showed hemodynamically significant stenosis (HSS) – narrowing $\geq 50\%$ of lumen of coronary arteries.

Statistical methods

Statistical analysis was performed by SPSS software for Windows (Version 17.0). Continuous variables were presented as mean and categorical variables as frequency and percentage. Comparisons between groups were performed using the Pearson chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables. Specificity, sensitivity and accuracy were analysed and Receiver Operating Characteristic (ROC) curve analysis was performed in order to evaluate predictive value of ECG stress test. The area under the ROC curve (AUC) was determined.

Table 1.
Characteristics of the whole study group

	Total (n = 2803) Mean ± SD	Women (n = 1666) Mean ± SD	Men (n = 1137) Mean ± SD	p
Age (years)	53.86 ± 6.28	57.59 ± 4.33	48.37 ± 4.38	<0.001
Arterial hypertension (%)	95.1	95.8	94.2	0.065
Dyslipidemia (%)	99.7	99.7	99.8	0.708
Diabetes mellitus (%)	20.1	21.9	17.6	0.006
Obesity (BMI ≥ 30 kg/m^2) (%)	62.8	63.2	62.3	0.649
Current smokers (%)	24.6	14.2	39.8	<0.001
Family history (%)	30.8	33.1	27.7	0.004
Left ventricular hypertrophy (%)	64.8	71	58.4	<0.001
Waist circumference (cm)	105.5 ± 10.5	103.1 ± 10.4	108.9 ± 9.7	<0.001
BMI (kg/m^2)	31.8 ± 6.9	32 ± 4.7	31.5 ± 4	<0.001
Total cholesterol (mmol/l)	6.50 ± 1.42	6.65 ± 1.40	6.28 ± 1.41	<0.001
LDL-C (mmol/l)	4.22 ± 1.21	4.41 ± 1.20	3.93 ± 1.16	<0.001
HDL-C (mmol/l)	1.20 ± 0.29	1.29 ± 0.29	1.07 ± 0.25	<0.001
TG (mmol/l)	2.39 ± 2.29	2.03 ± 1.34	2.92 ± 3.14	<0.001
Asymptomatic (%)	47.8	37.8	47.8	<0.001
Dyspnea (%)	13.9	18.8	6.8	<0.001
Typical anginal chest pain (%)	1.8	2	1.5	0.353
Atypical anginal chest pain (%)	5.6	7.5	2.8	<0.001
Non-anginal chest pain (%)	19.5	20.7	17.8	0.090

BMI – body mass index, LDL-C – low density lipoprotein cholesterol, HDL-C – high density lipoprotein cholesterol, TG – triglycerides.

Results

Baseline characteristics

Subjects of the study were 1666 (59.4%) women (the mean age is 57.59 years, SD ±4.33) and 1137 (40.6%) men (the mean age is 48.37 years, SD ±4.38) with MS and without the presence of CHD. Patients with symptoms consisted of 1208 (43.2%) patients – 845 (70%) women and 363 (30%) men. Second group included 1104 patients (47.8%) – 514 (46.6%) women and 590 (53.4%) men. Detailed baseline characteristics are summarized in Table 1.

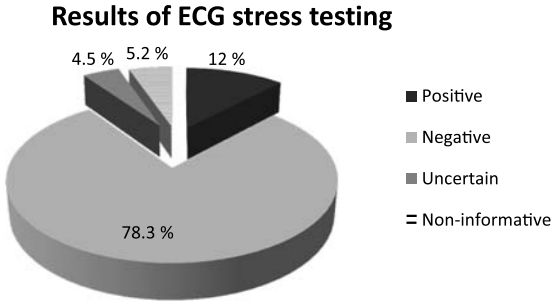

Figure 1. Results of electrocardiogram stress testing.

ECG stress testing results

ECG stress testing was performed in 2803 patients – 1666 (59.4%) women and 1137 (40.6%) men. Results were positive in 336 (12%) patients – 241 (71.7%) women and 95 (28.3%) men; uncertain or negative in 2321 (82.8%) patients – 1362 (58.7%) women and 959 (41.3%) men (Fig. 1).

In 146 (5.2%) cases the sub-maximal workload was not achieved and ECG exercise testing was rated as non-informative. Main reasons to stop the ECG exercise testing in those cases were leg fatigue (51.4%). Coronary angiography after ECG stress testing was performed in 56 (2%) patients (64.3% patients after positive ECG stress testing and 35.7% patients after negative or uncertain) and 17 (30%) HSS were found. CCTA after ECG stress testing was accomplished in 143 (5.1%) patients (49% after positive ECG stress testing and 51% after negative or uncertain) and 30 (21%) HSS were found. Results are summarized in Fig. 2.

Analysis of Receiver Operating Characteristic (ROC) curves showed that the area under ROC curve (AUC) was only 0.46 while determining HSS by coronary angiography and 0.5 while determining HSS by CCTA. These numbers show a very low ECG exercise testing diagnostic value.

In this study HSS was found in 47 cases, however 2 patients underwent both coronary angiography and CCTA, therefore CHD was diagnosed only in 45 patients (1.6%) given that 23 (51.1%) patients had positive ECG exercise testing.

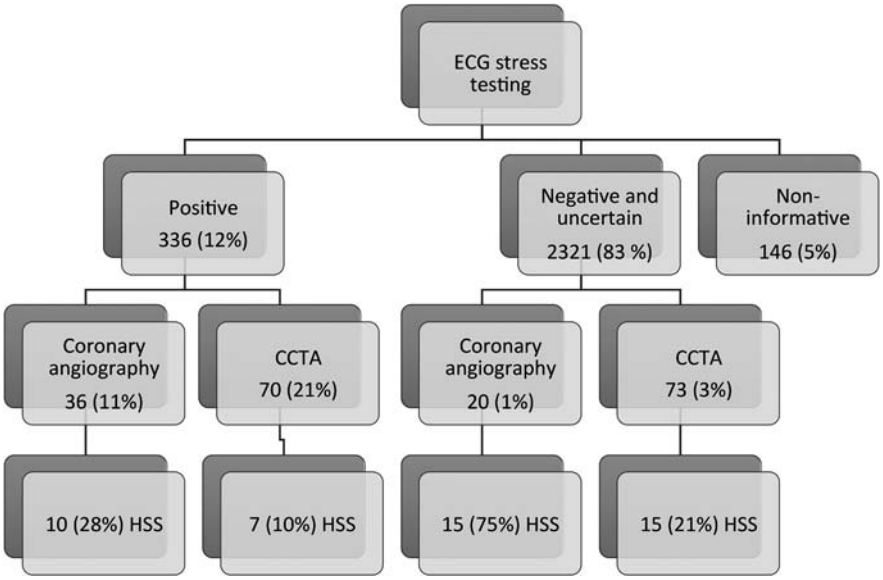

Figure 2. Results of electrocardiogram (ECG) stress testing, coronary angiography and coronary computed tomography angiography. CCTA – coronary angiography and coronary computed tomography angiography; HSS – hemodinamically significant stenosis.

Table 2.
The comparison of the prevalence of the positive ECG stress testing and CHD diagnosis in symptomatic and asymptomatic patients

Positive	Total (%)		Women (%)		Men (%)	
	1 group	2 group	1 group	2 group	1 group	2 group
ECG stress testing	16.6	8.9[$]	18.9	11[$]	10.8	7
CHD diagnosis	6.1	0.7[$]	5.3	0.6[$]	8	0.8[$]

ECG – electrocardiogram; CHD – coronary heart disease; 1 group – symptomatic patients, 2 group – asymptomatic patients; [$] p value < 0.001.

ECG exercise testing and symptoms

ECG stress testing was more frequently positive in patients, who had typical/atypical anginal chest pain, dyspnea and/or non-anginal chest pain, in comparison with asymptomatic patients (16.6% vs 8.9%, $p < 0.001$, in women respectively 18.9% vs 11%, $p < 0.001$, in men respectively 10.8% vs 7%, $p = 0.05$). CHD was more frequently diagnosed in symptomatic patients compared to patients without any symptoms (Tables 2 and 3).

After performing CCTA and coronary angiography in patients with and without symptoms, frequency of HSS was not statistically significant comparing both groups.

Discussion

Our study has determined very low diagnostic value of the ECG stress test for detecting CHD in patients with MS. It is assumed that in general about half of subjects with MS have a moderately high or high risk of developing CHD [20]. Although, our study enrolled patients with MS having only moderate to high CHD risk, screening with ECG stress test in these subjects appeared to be limited. This may be explained in several ways. First, the accuracy of ECG stress test, when it is based only on the ST-segment changes, is known to be limited [18]. Moreover, ECG stress test is associated with high rate of false-positive results, as mentioned below [7,15]. In addition, ECG exercise testing is more often false-positive in women compared to men because of the lower presence of CVD in women population [21]. It should be taken into account because most of the participants in our study were women (59.4%). Second, CHD prevalence in this population was very low, and majority of patients did not have typical anginal chest pain – that is the main reason of limited ECG stress testing diagnostic value.

Nevertheless, there are several reports suggesting ways for improving the predictive diagnostic value of ECG stress test. Kohli and Gulati noted that beside the ST-segment depression, there are other parameters, such as exercise capacity, blood pressure and chronotropic response, heart rate recovery and the Duke Treadmill Score, which increase the diagnostic and prognostic value of ex-

Table 3.
The prevalence of positive ECG stress test results and CHD depending on patient's symptoms

Positive test and CHD diagnosis	Total (%)		Women (%)		Men (%)	
	Dyspnea +	Dyspnea –	Dyspnea +	Dyspnea –	Dyspnea +	Dyspnea –
Positive ECG stress test	21.1	11.6$^{\$}$	21.2	14.7*	20.7	7.6*
CHD	6.5	3.1*	5.5	3.1	10.8	3*
	Typical anginal CP +	Typical anginal CP –	Typical anginal CP +	Typical anginal CP –	Typical anginal CP +	Typical anginal CP –
Positive ECG stress test	43.6	12.4$^{\$}$	40.7	15.4$^{\$}$	50	7.9$^{\$}$
CHD	24.4	3.2$^{\$}$	22.2	3.2$^{\$}$	28.6	3.2*
	Atypical anginal CP +	Atypical anginal CP –	Atypical anginal CP +	Atypical anginal CP –	Atypical anginal CP +	Atypical anginal CP –
Positive ECG stress test	30.1	11.9$^{\$}$	32.3	14.6$^{\$}$	20.8	8.1*
CHD	15.5	2.8$^{\$}$	13.7	2.7$^{\$}$	22.2	3$^{\$}$
	Non-anginal CP +	Non-anginal CP –	Non-anginal CP +	Non-anginal CP –	Non-anginal CP +	Non-anginal CP –
Positive ECG stress test	13	12.9	15.5	16	8.8	8.4
CHD	6	3*	5.3	3.1	7.1	2.8$^{\$}$

ECG – electrocardiogram, CHD – coronary heart disease, CP – chest pain; $^{*}p$ value < 0.005, $^{\$}p$ value < 0.001.

ercise ECG, especially in women [22]. It is also emphasized that exercise capacity alone provides an additional prognostic information regarding CHD in both men and women [9]. Furthermore, Chang et al. have observed that coronary artery calcium score improved long-term CHD risk stratification beyond exercise stress test [23]. This suggest that combining coronary artery calcium score and ECG stress test may lead to a better diagnostic evaluation for CHD [24]. Another recent study demonstrated that QT hysteresis (a phenomenon when the QT interval adapts to heart rate changes with a delay known as QT hysteresis or QT lag) index enhances the diagnostic value for CHD of ECG stress test, when they are combined together [5].

A variety of other non-invasive tests are currently available to establish the diagnosis of CHD, such as stress echocardiography, cardiac magnetic resonance (CMR), single-photon emission computed tomography (SPECT) or CCTA. Their diagnostic value was examined and compared to ECG stress testing in several studies. It is confirmed that stress echocardiography is superior to exercise ECG test due to its higher accuracy [25–27]. However, Grünig et al. stated that stress echocardiography adds little diagnostic information to ECG stress testing findings in unselected outpatients and it should not replace ECG stress test in cardiac screening [28]. Moreover, ECG stress testing may be initial diagnostic method in patients with chest pain having normal baseline ECG and functional capacity, whereas stress echocardiography may be more preferred in cases with abnormal baseline ECG and inability to exercise [29]. The diagnostic accuracy of SPECT has been also recognized to be superior to that of ECG stress testing (86.3% vs. 80.3%) [30], as well as the prognostic value of CCTA [31,32]. The CT-COMPARE study demonstrated the positive predictive value of CCTA to be higher comparing it with exercise ECG testing value in patients with acute chest pain [33]. However, the latest PROMISE study showed that an initial strategy of CCTA performing in symptomatic patients instead of functional testing was not associated with better clinical CHD outcomes [34]. Another non-invasive method, CMR stress perfusion imaging, was also determined to have higher accuracy for the evaluation of significant coronary obstruction compared to ECG stress testing [35]. Finally, it is of interest that among patients, referred for chest pain, cardiopulmonary exercise testing appeared to be more specific than standard ECG stress testing in predicting CHD outcome [36].

Our study has also investigated diagnostic value of the ECG stress testing for CHD depending on the presence of symptoms in patients with MS. The present study demonstrated that ECG stress testing was more frequently positive for patients with MS having typical/atypical anginal chest pain, dyspnea and/or non-anginal chest

pain in comparison with asymptomatic patients. Our finding is consistent with the previous study, which observed that typical angina is a strong predictor for a positive ECG stress test result [37]. Moreover, it was admitted that the main conditions of MS, such as impaired glucose tolerance, dyslipidemia, obesity or inflammatory syndrome have no significant influence on the ECG stress testing results [37,38].

Although it is reported that asymptomatic male patients with more than one CHD risk factor may receive useful prognostic information from ECG stress testing [18,39], our findings show that after screening subjects with ECG stress testing, who had MS, chest pain or dyspnea, CHD was diagnosed more frequently compared with asymptomatic patients.

Conclusions

In conclusion, this study presented that the diagnostic value of ECG stress testing for detecting CHD is limited in population with MS. Moreover, after exercise stress testing in patients with MS, who had anginal and non-anginal chest pain or dyspnea, CHD was more frequently diagnosed compared with asymptomatic patients. These findings show the importance of symptoms evaluation in MS patients before accomplishing ECG stress testing and improving its value.

Acknowledgement

This research is funded by the European Social Fund under the Global Grant measure (VP1-3.1-ŠMM-07-K-03-041).

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