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The modified protocol of transesophageal atrial pacing in stress echocardiography as an alternative way to increase the information value of the method for detection of ischemic wall motion abnormalities

Aim	To develop a new, modified protocol for transesophageal atrial electric stimulation (TEAES), which would significantly enhance the diagnostic value of stress echocardiography and reduce the duration of the test in patients with ischemic heart disease (IHD).
Material and methods	This study included 101 patients (80 men and 21 women aged 55±9 years) with suspected or documented diagnosis of IHD who were divided into two homogenous groups. Group 1 (51 patients) underwent stress echocardiography (stress-EchoCG) according to a standard protocol (SP) for TEAES and group 2 (50 patients), underwent stress-EchoCG according to a modified protocol (MP). In addition to stress-EchoCG with TEAES, selective coronary angiography was performed for all patients. The development of the new method for evaluating occult coronary insufficiency was based on comparison of SP and MP for TEAES with stress-EchoCG with data of coronary angiography.
Results	In both groups, significant differences in values of systolic and diastolic blood pressure were absent. However, the values of achieved heart rate were significantly different: 141±11 (TEAES SP) and 155±10 (TEAES MP) bpm (p=0.01). There was also a difference in the duration of the TEAES protocols: 15±3 and 5±2 min, respectively (p=0.006). The use of the modified TEAES protocol for detecting transient disorders of left ventricular myocardial local contractility increased the sensitivity, specificity and accuracy of the test from 76%, 87%, and 80% to 83%, 92%, and 86%, respectively. The most significant differences were found in the area supplied by the circumflex artery: the SP and MP sensitivities were 63% and 75%, respectively (p<0.05) and the SP and MP accuracies were 81% and 90%, respectively (p<0.05).
Conclusion	Evaluation of occult coronary insufficiency by stress-EchoCG with the TEAES MP as compared to the TEAES SP provides a gentler procedure regimen for the patient due to a shorter duration of the test and at the same time improves the diagnostic significance of this method in IHD patients.

Keywords	Ischemic heart disease; stress-echocardiography; transesophageal atrial electric stimulation; myocardial ischemia
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Introduction

Coronary artery disease (CAD) is one of the most frequent causes of death in the developed countries, including the Russian Federation. Non-invasive imaging stress tests should be treated as the first-line diagnosis of CAD in patients with chest pain [1]. The preferred technique is stress ech ocardiography, which is a fusion of two-dimensional echocardiography and various types of stress testing [2].

Electrocardiographic stress tests (bicycle ergometry, treadmill test) have less diagnostic value, which produces many false-positive and false-negative results. These tests are recommended if imaging techniques are not available, and for the diagnosis of heart rhythm disorders during stress, the evaluation of exercise tolerance, and the efficacy of antianginal therapy in patients with CAD [1].

Stress echocardiography is well tolerated and has a lower cost compared to such methods as myocardial perfusion scintigraphy and multislice computed tomography angiography, which allows reducing patient examination costs and, if necessary, performing multiple re-examinations [2]. The advantages of stress echocardiography over myocardial perfusion scintigraphy also include higher specificity (espe-

cially in patients with left bundle branch block), safety due to lack of radiation exposure, and the possibility to evaluate transient myocardial ischemia in real time [3, 4]. Stress myocardial perfusion scintigraphy is more sensitive (especially in single-vessel disease of the left circumflex artery) and accurate in multiple abnormalities of left ventricular (LV) wall motion at rest [5].

Physical exercises (vertical and horizontal bicycle ergometry, treadmill test), pharmacological tests (dobutamine, dipyridamole, adenosine), pacing tests, and transesophageal atrial pacing (TAP) are the most common stress tests used in echocardiography [6].

Each test has its features, advantages, and disadvantages. Physical exercises provoke ischemia with the increased myocardial oxygen demand. Its advantages are simplicity, adjustment to human physiology, high tolerability, and the ability to assess the cardiovascular response to stress. The disadvantages include difficulties obtaining high-quality images during stress tests and the inability to perform tests in specific populations (patients with severe dyspnea, lower extremity vascular disease, uncontrolled arterial hypertension, etc.) [7, 8].

Dobutamine (a synthetic catecholamine) selectively stimulates β1 receptors, enhances the inotropic and chronotropic activity of the heart, thereby increasing myocardial oxygen demand. The hemodynamic effects of its action are linearly correlated with the plasma levels of the drug. The half-life period is only 2 minutes, and small doses (up to 10–15 μg/kg/min) increase the myocardial wall motion and do not affect the heart rate significantly, which allows assessing myocardial viability and inotropic reserve [9, 10].

Dipyridamole is an arterial vasodilator. The mechanism of its action is based on the phenomenon of inter- and intracoronary steal, which occurs when the levels of endogenous adenosine increase. Injection of dipyridamole induces ischemia in the stenotic artery territory due to the preferential dilatation of the intact arteries and increased blood flow in the healthy myocardium [11].

The main advantages of pharmacological tests are higher-quality images of the heart, and particularly for dobutamine tests, the possibility of detecting the stunned and hibernating myocardium. The disadvantage is the more frequent occurrence of various heart rhythm disorders and blood pressure (BP) fluctuations during the test [8].

TAP and pacing tests are based on a step-by-step increase in heart rate (HR) until the target values or other criteria are met to stop the test [2]. In TAP, increased HR reduces the diastolic component of coronary blood flow and simultaneously increases myocardial oxygen demand, which causes the insufficient blood supply to the respective regions of the myocardium if there are narrowed coronary arteries [12]. Since BP changes insignificanlty during the stimulation, myocardial oxygen consumption increase, but not as significantly as during exercise. Therefore, TAP-associated ischemia is less severe and short-term. This type of testing is attractive by the controllability of the stimulation frequency and the possibility to stop the test quickly. In addition, there is no hyperventilation and effects on the peripheral vascular system [13]. TAP is possible in patients with high arterial hypertension (due to relatively stable BP), those with musculoskeletal diseases, lower extremity vascular diseases (intermittent claudication, varicose veins, thrombophlebitis), respiratory diseases, neurological disorders, deconditioned, and bed-bound patients. The disadvantage of TAP is relatively low sensitivity and discomfort for the patient, related directly to the stimulation [14].

According to the literature, TAP has an informative value comparable to pharmacological tests. TAP has higher sensitivity but lower specificity than dipyridamole test [15], less likely to cause such side effects as arterial hypertension and rhythm disorders than dobutamine test [16].

The most common standard protocol (SP) of TAP is a discrete, intermittent, step-wise increase in pacing frequency by 10–20 pulses every 2 minutes to a submaximal age-associated limit calculated using the formula 0.85 × (220 – patient age). In this case, the initial frequency of stimulation is usually 100–110 ppm or higher than the own rhythm by 10 ppm. The examination usually lasts for 12 to 20 minutes. (Figure 1A) [12].

This method has a rather high specificity (83–90% according to different data) and relatively low sensitivity (70–76%) [15, 17, 18] and reproducibility (52%) [15], which can be explained by various factors. Given that ischemia is relatively moderate in TAP, stimulation at the submaximal frequency may not be sufficient for the reliable evaluation of the results of examination [19, 20]. Intermittent stimulation will cause more prolonged discomfort for the patient and may also reduce the informative value of the method, which is why it is necessary to develop a modified protocol (MP) of TAP.

Aim

Develop a new TAP MP to increase the diagnostic value of stress echocardiography and reduce the duration of the examination in CAD patients.

Material and methods

The study included 101 patients (81 male and 20 female, mean age 55±9 years) with suspected or documented CAD who were divided into two homogeneous groups (Table 1):

- 51 patients subjected to stress echocardiography using the standard TAP protocol.
- 50 patients subjected to stress echocardiography using the modified TAP protocol.

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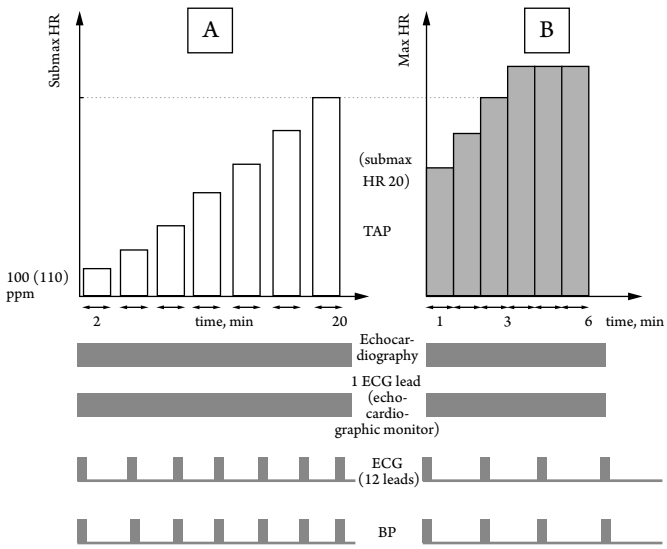
Figure 1. Standard (A) and modified (B) TAP in stress echocardiography for the detection of latent coronary artery disease [21]



TAP, transesophageal atrial pacing; submax HR, heart rate; max HR, maximum heart rate; ECG, electrocardiogram, BP, blood pressure.

Table 1. Demographic characteristics of patients included in the study

Parameters	Study groups		
	Standard protocol, n=51	Modified protocol, n=50	p
Male/female, n (%)	40 (78)/ 11 (22)	40 (80)/ 10 (20)	>0.05
Age, years	57±9	60±7	>0.05
BMI, kg/m^2	29.7±4.6	29.0±4.3	>0.05
Known CAD, n (%)	63	62	>0.05
Coronary atherosclerosis according to CAG, total, n (%)	37 (72)	28 (56)	>0.05
LAD involvement, n (%)	23 (45)	28 (56)	>0.05
RCA involvement, n (%)	20 (39)	16 (32)	>0.05
LCX involvement, n (%)	19 (37)	12 (24)	>0.05

CAD, coronary artery disease; BMI, body mass index; CAG, coronary angiography; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

All patients signed informed consent to be included in the study. The study design was approved by the Ethics Committee.

The new method for evaluating latent coronary insufficiency (LCI) was based on the comparison of the modified and standard protocols of stress echocardiography with CAG data.

Preparation for the study: the test was performed fasting in the morning or 3 to 4 hours after the meal; it was recommended discontinuing antianginal drugs 48 to 72 hours before the examination, excluding smoking, and avoiding significant physical load within the immediate 6 hours. The oropharynx was anesthetized before the examination with a 10% lidocaine solution to suppress the vomiting reflex and reduce discomfort when the electrode probe is inserted.

TAP was conducted using an automated Cardiac EDI – Astrocardium complex (Meditek, Russia) with a pacemaker, and cardiac ultrasound examination was performed using an expert-class IE-33 device (Philips, Germany).

Protocol of the examination

1. The patient is placed on the couch in the left lateral position, 12-lead ECG is performed, and BP is measured. The echocardiographic images are recorded at rest via the parasternal access along the long and short LV axes and the apical access in four-, two- and three-chamber views.
2. After antiseptic treatment and rinsing with distilled water, the TAP electrode probe is slowly inserted through the mouth into the esophagus lumen for 30–40 cm. The patient is asked to tilt the head forward and make small swallowing movements. The electrode is then connected to the pacemaker: proximal contact to the negative terminal and distal contact to the positive terminal.
3. Then, the electrode is finally installed using a transesophageal electrocardiogram (ECG) to achieve the maximum positive amplitude of the P wave.
4. The pacemaker is set to a frequency higher than the patient's rhythm by 10 ppm. The test atrial pacing is initiated from 13–15 V. Stable pacing is achieved by gradually increasing the amplitude of the pulses. The stimulation threshold is usually not higher than 15–22 V.
5. Transesophageal atrial stimulation starts at the rate of 20 beats less than the submaximal HR. The stimulation frequency is increased continuously by 10 ppm every minute until the maximal HR is reached (220 – the patient's age) (Figure 1B). The maximal HR stimulation continues for 3 minutes. If atrioventricular block grade 2 with the Wenckebach periods develops, atropine sulfate 1 mg is administered intravenously.
6. During TAP and in the first minutes after its termination, continuous ECG (12-lead) is recorded, BP is monitored, and ventricular wall motion is assessed using echocardiography in the five standard views described in paragraph 1.

Diagnostic criteria for the test discontinuation are achieving the maximal HR and the occurrence of transient LV wall motion abnormalities.

Statistical analysis

The following formulas were used to calculate the informative value of the diagnostic test (sensitivity, specificity, accuracy):

$$\text{Sensitivity}=TP/(TP+FN)\times 100\%;$$
$$\text{Specificity}=TN/(TN+FP)\times 100\%$$
$$\text{Accuracy}=(TP+TN)/(TP+TN+FP+FN)\times 100\%,$$

Where TP is the true-positive test result, TN is the true-negative result, FP is the false-positive result, and FN is the false-negative test result.

The statistical processing of the data was performed using Statistica 10.0 (StatSoft, USA). The results of the normally distributed parameters were presented as M±SD. The differences were considered statistically significant at $p<0.05$. In the case of normal distribution, the data were compared using the Student's t-test. The Shapiro–Wilk test was used to test the normality of the distribution of quantitative traits, and the two-tailed Fischer's exact test was used to determine the significance of differences between the qualitative traits.

Results

There were no significant differences in SBP and DBP in both groups, but there was a statistically significant difference in the achieved HR and the duration of the TAP protocol (Table 2).

The modified TAP protocol to detect transient LV wall motion abnormalities increased the sensitivity, specificity, and accuracy of stress echocardiography from 76, 87, and 80% to 83, 92, and 86%, respectively.

The segmental evaluation of transient LV wall motion abnormalities used in the proposed technique of stress echocardiography allowed determining the symptom-related artery with high accuracy (Table 3). The most significant differences were found in the territory of the left circumflex artery: sensitivity of the standard and modified protocols was 63 and 75% ($p<0.05$), respectively, and the accuracy was 81 and 90% ($p<0.05$), respectively.

Table 2. Characteristics of patients in stress echocardiography in the standard and modified TAP protocol groups

Parameters	Study groups		
	Standard protocol, n=51	Modified protocol, n=50	p
SBP baseline, mmHg	138±27	143±20	>0.05
SBP max, mmHg	157±30	161±19	>0.05
DBP baseline, mmHg	82±10	89±8	>0.05
DBP max, mmHg	89±17	93±10	>0.05
HR baseline, bpm	66±12	63±12	>0.05
HR max, bpm	141±11	155±10	< 0.05
Transient LV WMAs, total, n (%)	28 (59)	22 (50)	>0.05
LAD WMAs, n (%)	16 (33)	22 (50)	>0.05
RCA WMAs, n (%)	16 (37)	13 (32)	>0.05
LCX WMAs, n (%)	12 (28)	9 (22)	>0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; WMA, wall motion abnormality; LV, left ventricle; LAD, left anterior descending artery; RCA, right coronary artery; LCX, left circumflex artery.

Discussion

Our protocol, unlike the prototype, includes the following:

- Step-wise discrete increasing TAP is performed continuously.
- The initial stimulation frequency is set based on the submaximal HR reduced by 20 ppm.
- At the last step, TAP is carried out at the maximal HR (corresponding to the age) for 3 minutes.
- The maximum protocol duration is 6 minutes (Figure 1B).

The development of the modified TAP protocol has made it possible to correct many drawbacks of the standard protocol.

First, unlike intermittent stimulation, continuous stimulation prevents the cardiovascular system from using its adaptive capabilities, which leads to the regression of ischemia in patients with hemodynamically significant coronary stenosis.

Second, the coronary reserve in the affected artery decrease with shorter diastole as the heart rate increases [20]. In other words, the higher the heart rate is, the shorter is the diastole and the smaller is the coronary reserve, and therefore achieving the maximal HR, unlike the submaximal HR, leads to higher myocardial oxygen demand and results in the development of more severe ischemia.

These factors allow significantly increasing the informative value of stress echocardiography with TAP: sensitivity, specificity, and accuracy of the technique increased to 83, 92, and 86%, respectively). The sensitivity of the technique was also increased in detecting latent coronary insufficiency in the territory of LAD (up to 79%) and LCX (up to 75%), as well as the accuracy of the technique for LCX (up to 90%).

Moreover, the duration of stimulation using the modified protocol is two times shorter than with the standard protocol, which reduces the patient's discomfort

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Table 3. Diagnostic significance of stress echocardiography using standard and modified protocols of TAP

	n	CAG			LAD			LCX			RCA		
		S	Sp	A	S	Sp	A	S	Sp	A	S	Sp	A
SP	51	76*	87	80	70*	96	84	63*	92	81*	80	90	84
MP	50	83*	92	86	79*	91	85	75*	95	90*	81	91	88

* p<0.05. SP, standard protocol; MP, modified protocol; CAG, coronary angiography; LAD, left anterior descending artery; LAD, left anterior descending artery; RCA, right coronary artery; S, sensitivity; Sp, specificity; A, accuracy.

associated with the stimulation. Thus, the modified protocol is a faster and more informative technique of TAP. The Russian patent was obtained for this technique in 2013 [21].

Conclusion

Evaluation of latent coronary insufficiency in stress echocardiography using the modified TAP protocol compared to the analogs allows the examination to be conducted more comfortably for patients by reducing the test duration and increasing the diagnostic significance of the technique in CAD patients.

No conflict of interest is reported.

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