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SHORTNESS OF BREATH ON EXERTION: DIAGNOSTIC POSSIBILITIES OF STRESS ECHOCARDIOGRAPHY

<i>Aim</i>	To determine diagnostic capabilities of the expanded protocol for stress echocardiography (stress-EchoCG) with comprehensive evaluation of clinical and echocardiographic indexes in differential diagnosis of dyspnea.
<i>Material and methods</i>	This study included 243 patients (123 women and 120 men) who were referred to outpatient stress-EchoCG during one calendar month. For 80 patients complaining about shortness of breath, the expanded stress-EchoCG protocol with treadmill exercise was performed. During the exercise, E/e' and tricuspid regurgitation velocity were determined, and clinical features and possible nature of dyspnea were evaluated.
<i>Results</i>	Shortness of breath had an ischemic origin in 17.5% of 80 patients; 13.8% had criteria of elevated left ventricular end-diastolic pressure; 17.5% of patients had clinical signs of bronco-pulmonary pathology; 5.0% had moderate and severe mitral regurgitation; 20% displayed signs of chronotropic insufficiency during exercise including on the background of beta-blocker therapy; 15.0% of patients displayed a hypertensive response to exercise, which was associated with signs of chronotropic insufficiency in 50% of them; and 1.3% had signs of hyperventilation syndrome. In addition to diagnosis of transient ischemia, additional information about the nature of shortness of breath was obtained for 72.5% of patients. Based on results of the test, objective causes for dyspnea were not identified for 10.0% of patients.
<i>Conclusion</i>	The expanded stress-EchoCG protocol with exercise allows obtaining information about the nature of dyspnea for most patients with shortness of breath of a non-ischemic origin. For this patient category, expanding the stress-EchoCG protocol does not increase duration of the study and is economically beneficial for diagnosis of chronic heart failure and other causes for shortness of breath.
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Introduction

Exercise-stress echocardiography (ESE) is a test commonly used to identify transient myocardial ischemia and stratify the risk in patients with verified coronary artery disease (CAD). At the same time, the great variety of cardiac pathologies requires the administration of ESE in patients without CAD and exertional angina pectoris. For example, one of the frequent reasons for ordering ESE is dyspnea complained of by almost 25% of patients at an outpatient cardiology visit [1] and almost 9.9% of patients at a general practitioner appointment [2].

The very notion of dyspnea is complex and has many aspects. As suggested by the American Thoracic Society, dyspnea is a subjective experience of breathing discomfort that consists of qualitatively distinct sensations varying in intensity and which may or may not be accompanied by objective respiratory disorders [3]. The famous Russian

physician of the first half of the 20th century, D. D. Pletnev, spoke about the difficulties of interpreting complaints and possible dissonance between objective and subjective data: «It is difficult to define the term «dyspnea» precisely. It is difficult because it involves two phenomena at the same time: objective and subjective. In some cases, a patient complains of dyspnea, and a physician sees no relevant symptoms, except for the patient's complaints. And vice versa, there may be objective symptoms of dyspnea (more frequent or rarer and deeper breathing, cyanosis), while the patient does not complain of dyspnea». In some cases, a detailed inquiry about dyspnea will provide the key to understanding its origin [4]. Use of the special «language» of dyspnea («difficulty breath in/out», «out of breath», «frequent breathing», «choking in», «air hunger», «heavy breathing», «shallow breathing») allows an experienced physician to presume the cluster of the

disease that caused it and determine the algorithm for diagnosis and treatment [5]. However, many expensive and sometimes unsafe examinations are often required, in order to determine the cause of dyspnea.

Patients with dyspnea are known to have a worse prognosis than those with chest pain [6], but the incidence of transient myocardial ischemia is only about 10% [7]. ESE in patients with dyspnea of a non-ischemic nature provides the opportunity to specify the hemodynamic conditions of a variety of valvular heart defects and cardiomyopathy, as well as to evaluate left ventricular (LV) diastolic function and pulmonary artery systolic pressure (PASP) with exercise [8]. The diagnosis of chronic heart failure (CHF) with preserved left ventricular ejection fraction (LVEF) is based on clinical, laboratory data (natriuretic peptide levels, such as BNP, NT-proBNP), and echocardiographic measurements at rest [9]. This includes LV hypertrophy, enlarged left atrium, and markers of the elevated left ventricular end-diastolic pressure (LVEDP) – E/e' , i.e., the ratio of the E transmitral peak velocity measured with the pulse-wave Doppler mode to the myocardial velocities in the medial and lateral mitral annulus, acquired in the tissue Doppler mode. In patients with dyspnea without CHF criteria with preserved LVEF and E/e' from 8 to 13, it is reasonable to perform a so-called diastolic stress test and evaluate these parameters with exercise. A clinically significant increase in E/e' or E/e' septal indirectly indicates a hemodynamically significant increase in LVEDP with exercise. It can serve as a criterion for a positive diastolic stress test [10]. The tricuspid regurgitation velocity of more than 2.8 m/s and registration of B-lines in the lungs with exercise provides additional valuable information in this test.

In patients without documented myocardial ischemia and CHF with preserved LVEF, dyspnea may be caused by valvular heart defects, dynamic obstruction of the LV outflow tract, hypertensive reaction to load, and chronotropic incompetence (CI).

Of the extracardiac causes, the first is bronchopulmonary pathology, which can also be suspected in ESE when evaluating the nature of dyspnea (inspiratory, expiratory, mixed), non-invasive pulse oximetry, and pathological increases in the tricuspid regurgitation velocity. These symptoms may be useful in determining methods for further diagnosis.

Finally, if the combination test and the set of additional clinical data do not identify the organic cause of dyspnea, the patient's deconditioning or a neurological cause of dyspnea can be assumed. It should be understood that one patient may have several causes of dyspnea at the same time, but the task for ESE is to try to highlight the main cause of dyspnea.

Objective

To determine the diagnostic capabilities of the advanced ESE protocol with a comprehensive evaluation of clinical and echocardiographic parameters in the differential diagnosis of dyspnea.

Material and methods

The study included 243 patients (123 females, 120 males) with verified or suspected CAD.

The inclusion criteria were indications for ESE following the 2008 guidelines of the European Association of Echocardiography (EAE), and the physical ability to perform a treadmill exercise. The exclusion criteria were the presence of contraindications to stress test (non-correctable arterial hypertension, untreated life-threatening ventricular rhythm disorders, moderate to severe valvular heart defects), dilatational and hypertrophic cardiomyopathy, pericardial effusion.

A third (33%) of the total patient sample had complaints of dyspnea with exercise.

Duration of the study. Patient recruitment and analysis of complaints during ESE were performed within 24 working days (from 18/10/18 to 22/11/18). In addition to the standard treadmill ESE, its features were specified, and a diastolic stress test was performed in 80 patients with complaints of dyspnea, in order to assess intracardiac and systemic hemodynamic changes with exercise and to determine the nature of dyspnea.

Clinical characteristics of patients are presented in Table 1.

The test was performed on a T2100 treadmill following the standard Bruce protocol. Systolic and diastolic blood pressure (BP) was measured on the left hand using the Korotkov method at each stage of the exercise ranging from 1 minute 30 seconds to 2 minutes from the beginning of each stage, and at the 2nd minute of the recovery period. Electrocardiogram (ECG) was recorded using the CardioSoft stress testing software.

A GE Vivid7 Dim 10S (1–3.5 Mhz) sensor was used to record pre- and post-load standard echocardiographic positions, transmitral flow in the pulsed-wave Doppler mode, septal and lateral annular velocities in the tissue Doppler mode, and tricuspid regurgitation velocity in the continuous-wave Doppler mode. The total record time for all images, including Doppler, was 1 to 1.5 minutes after stopping exercise.

The following clinical patterns were recorded: nature of dyspnea (inspiratory/expiratory); productive cough with exercise; hyperventilating syndrome defined as a feeling of incomplete inspiration, dissatisfaction with inspiration in the absence of objective signs of

respiratory failure, and decreased stress tolerance [11, 12].

The following stress test parameters were evaluated:

1. The adequacy of heart rate (HR) increase with exercise. The following CI criteria were accepted: patient's inability to reach 85% of the maximum age-specific HR, the maximum HR = (220 – age) bpm [13]; patient's inability to overcome the 80% HR reserve barrier calculated as:

$$\frac{(\text{reached HR} - \text{HR at rest})}{(\text{maximum HR} - \text{HR at rest})} [14].$$

2. The type of BP response to the load. The following criteria of hypertensive reaction to load were used: systolic BP ≥ 190 mm Hg in female patients, ≥ 210 mm Hg in male patients [15], or ≥ 180 mm Hg from the second stage of load regardless of gender [16].

During the echocardiographic examination at rest, the presence and degree of mitral and tricuspid regurgitation were evaluated before exercise in accordance with the American Society of Echocardiography guidelines for the evaluation of valve regurgitation [17], tricuspid regurgitation velocity, and LV diastolic performance. E/e' was calculated at rest in some patients, and others underwent additional calculations with exercise if E/e' was the gray zone (8–13).

The following values were used as the criteria for increased LVEDP at rest: E/e' ≥ 13 , E/e'septal ≥ 15 , E/e'lateral ≥ 12 [10].

The following values were accepted as the criteria for increased LVEDP with exercise: E/e' > 14 , E/e'septal > 15 [8].

Tricuspid regurgitation and its gradient were assessed at rest and with exercise from apical access and the sensor moving toward the right chambers of the heart. The regurgitation velocity at rest > 2.8 m/s and/or PASP > 40 mm Hg were pathological, as well as the increase in PASP ≥ 60 mm Hg with exercise. PASP was calculated as the sum of the tricuspid regurgitation gradient and the right atrium pressure estimated during the subcostal imaging of the inferior vena cava [8].

The total duration of the examination with diastolic stress testing was not significantly increased.

Before the examination, patients signed informed consent for ESE. The results were analyzed retrospectively.

The data obtained was analyzed using Statistica 7.0 software suite. The normality of distribution was tested using the Shapiro – Wilk test. Continuous numerical data is presented as the median and interquartile range (Me [25th percentile; 75th percentile]), the qualitative and categorical variables are expressed as the percentage. The intergroup differences of the quantitative variables

were assessed using the Mann-Whitney U-test and the categorical and qualitative variables using the Pearson chi-square test and the Fisher exact test. The linear correlation of quantitative and qualitative variables was evaluated using the Spearman rank correlation coefficient $p < 0.05$.

Results

The analysis of complaints revealed that the reasons for stopping the test were dyspnea in 80 (32.9%) patients, chest pain and/or discomfort in 7 (2.9%) patients, dizziness in 8 (3.3%) patients, and general fatigue or lower limb fatigue in 42 (17.3%) patients. Dyspnea correlated with the patient's age ($r_s = 0.4$; $p < 0.05$). The findings are shown in Figure 1.

27 (11.1%) tests were positive for only the echocardiographic criteria, 11 (4.5%) tests were positive for both the electrocardiographic and echocardiographic criteria.

The submaximal HR was reached in 172 of 243 patients. The exercise tolerance in the study sample was 8.5 [6.0; 10.8]

Table 1. Clinical characteristics of the patients examined

Indicator	Included patients (n=243)	Patients with dyspnea (n=80)
Age, years	59.0 [51.0; 66.0]	65.0 [58.0; 70.5]
History of CAD	88 (36.2)	38 (47.5)
History of myocardial infarction	59 (24.3)	26 (32.5)
History of PCI	55 (22.6)	20 (25)
History of CABG	11 (4.5)	5 (6.25)
No history of arterial hypertension	65 (26.7)	6 (7.5)
Hypertensive heart disease without indication of TOD and ACC	8 (3.3)	1 (1.25)
Hypertensive heart disease with indication of TOD	80 (32.9)	28 (35)
Hypertensive heart disease with indication of ACC	90 (37.0)	45 (56.3)
Diabetes mellitus type 2	26 (10.7)	14 (17.5)
CHF FC II	11 (4.5)	8 (10.0)
CHF FC III	12 (4.9)	10 (12.5)
Bronchopulmonary pathology	11 (4.5)	8 (10.0)
ESE on the top of treatment		
Thiazide diuretics	34 (14.0)	19 (23.8)
Loop diuretics	13 (5.3)	9 (11.3)
Beta-blockers	111 (45.7)	52 (65.0)
Verapamil	1 (0.4)	1 (1.25)

The data is presented as the median and interquartile range (Me [25th percentile; 75th percentile]) or the absolute numbers. CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; ACC, associated clinical conditions; TOD, target organ damage; CHF, chronic heart failure; FC, functional class; ESE, exercise-stress echocardiography.

METs with the duration of 436.0 [273.0; 574.0] sec – both were negatively correlated with patient age ($r_s = -0.6$ and $r_s = -0.62$, respectively; $p < 0.05$). Dyspnea was negatively correlated with exercise tolerance ($r_s = -0.45$; $p < 0.05$).

The clinical characteristics of 80 patients (49 females, 31 males) with dyspnea during ESE are given in Table 1. The submaximal HR was reached in 55 (68.8%) of 80 patients. There was no significant correlation between beta-blocker use and the submaximal HR in patients with dyspnea ($r_s = -0.18$; $p > 0.05$), unlike in the general sample ($r_s = -0.34$; $p < 0.05$). Exercise tolerance was 5.5 [4.6; 8.5] METs with duration of 252.0 [180.0; 421.0] sec. The reasons for stopping the test, along with achieving the submaximal HR and dyspnea, were chest pain and/or discomfort in 6 (7.5%) patients, dizziness in 5 (6.25%) patients, and general fatigue or lower limb fatigue in 29 (36.3%) patients.

ESE was positive in terms of the echocardiographic criteria in 14 (17.5%) of 80 patients with dyspnea. 5 of them

also had electrocardiographic criteria for a positive result (Figure 2).

The rate of positive tests in patients with dyspnea did not differ from the rate of positive results in the general sample ($\chi^2 = 0.15$; $p = 0.69$) and patients without dyspnea ($\chi^2 = .31$; $p = 0.58$). Based on the Doppler assessment of transmitral blood flow, septal and lateral mitral annular diastolic velocities in the tissue Doppler mode, and tricuspid regurgitation velocity at rest and with exercise, criteria for the elevated LVEDD at rest and/or with exercise were obtained in 11 (13.8%) of 80 patients. This made it possible to establish CHF as the cause of dyspnea. E/e' at rest and with exercise and PASP at rest increased with age ($r_s = 0.43$, $r_s = 0.82$, and $r_s = 0.42$, respectively; $p < 0.05$). Patients with a history of CAD ($r_s = 0.37$, $p < 0.05$) and myocardial infarction ($r_s = 0.5$, $p < 0.05$) had higher E/e' values at rest. The E/e' values at rest and with exercise were negatively correlated with exercise tolerance ($r_s = 0.43$ and $r_s = 0.67$, respectively; $p < 0.05$), and E/e' at rest was positively correlated with PASP at rest ($r_s = 0.33$; $p < 0.05$).

Figure 3 shows the echocardiographic findings in a 65-year-old female patient with verified CAD, complaints of dyspnea with preserved LVEF, negative ischemic and positive diastolic stress tests. Elevated mean E/e' to 15.5 reflects an increase in LVEDP and pulmonary circulation pressure with increased tricuspid regurgitation velocity with exercise up to 4.49 m/s in the continuous wave Doppler mode.

Figure 4 contained the diagrams of transmitral flow in the pulsed-wave Doppler mode and the septal and lateral mitral annular velocities in the tissue Doppler mode during in ESE in a 59-year-old female patient with CAD, dyspnea, a history of revascularizations, reduced LVEF to 45% (Simpson), and negative results in both tests. E/e' equal to 11.8 indicates that there is no evidence of an increase in LVEDP with exercise.

Of the remaining patients with dyspnea, 14 (17.5%) had clinical signs of bronchopulmonary pathology such as expiratory dyspnea, productive cough during and after exercise, and/or a pathological increase in the tricuspid regurgitation velocity with exercise, without worsening of the LV diastolic function. The color Doppler echocardiography revealed grade II or III mitral regurgitation (at rest and/or dynamic) in 4 (5.0%) patients.

16 (20.0%) of patients had signs of CI during exercise, 13 of them had those signs on the top of using beta-blockers. At the same time, not all patients with criteria of CI complained of dyspnea. However, CI was significantly correlated with dyspnea in the general sample ($r_s = 0.48$; $p < 0.05$). Besides dyspnea, patients of the general sample with criteria of CI had fatigue with exercise ($r_s = 0.54$; $p < 0.05$) and received beta-blockers ($r_s = 0.33$; $p < 0.05$) more frequently.

Another 12 (15.0%) patients had a hypertensive reaction to load, which was considered as the main cause of

Figure 1. Causes for stopping the test

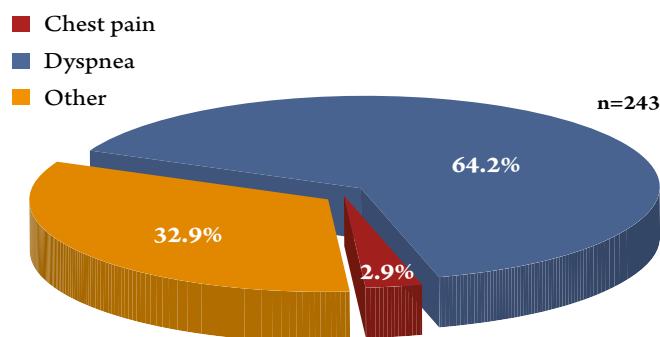
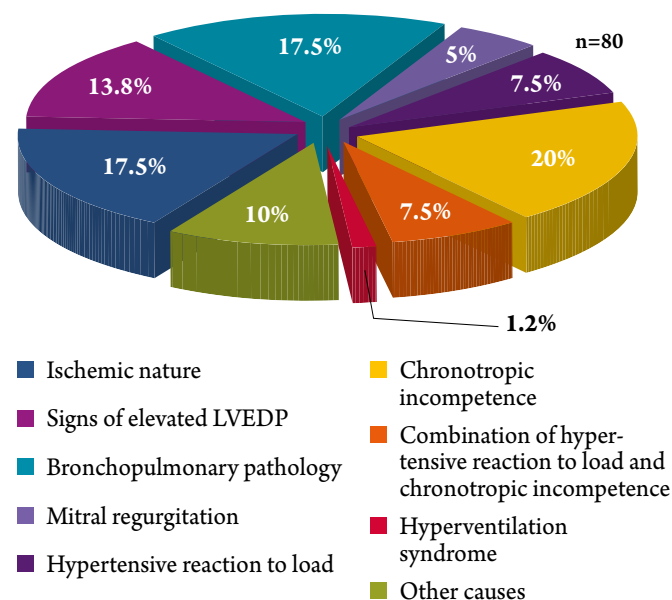
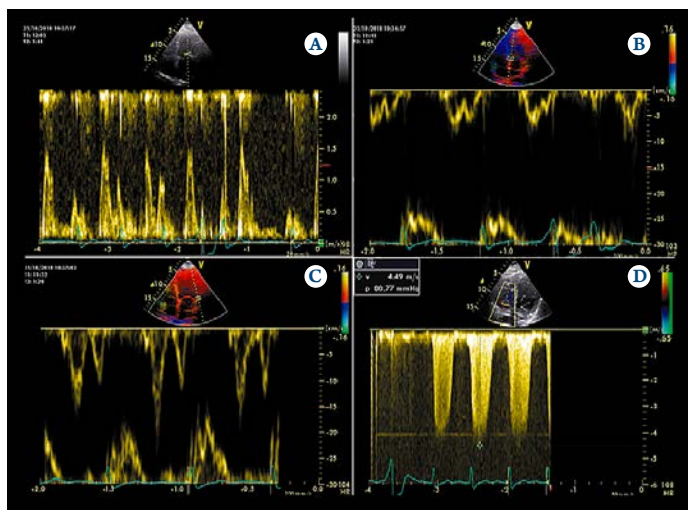


Figure 2. Expected cause of dyspnea resulting from the advanced ESE



LVEDP, left ventricular end diastolic pressure.

Figure 3. Echocardiogram of a 65 year-old female patient with coronary artery disease and complaints of dyspnea



A – E and A peaks of transmitral blood flow with exercise in the pulsed-wave Doppler mode; B, C – septal (B) and lateral (C) mitral annular diastolic velocities with exercise in the tissue Doppler mode; D – tricuspid regurgitation velocity with exercise in the continuous-wave Doppler mode.

dyspnea, and 7.5% of them had hypertensive reaction to load combined with signs of CI, which could be associated with the use of beta-blockers in 3 patients. Hypertensive reaction to load was negatively correlated with exercise tolerance ($r_s = -0.37$; $p < 0.05$). The cause of hypertensive reaction to load in 1 patient was hyperventilation syndrome, which occurred during the test combined with objectively high exercise tolerance (16.5 METs).

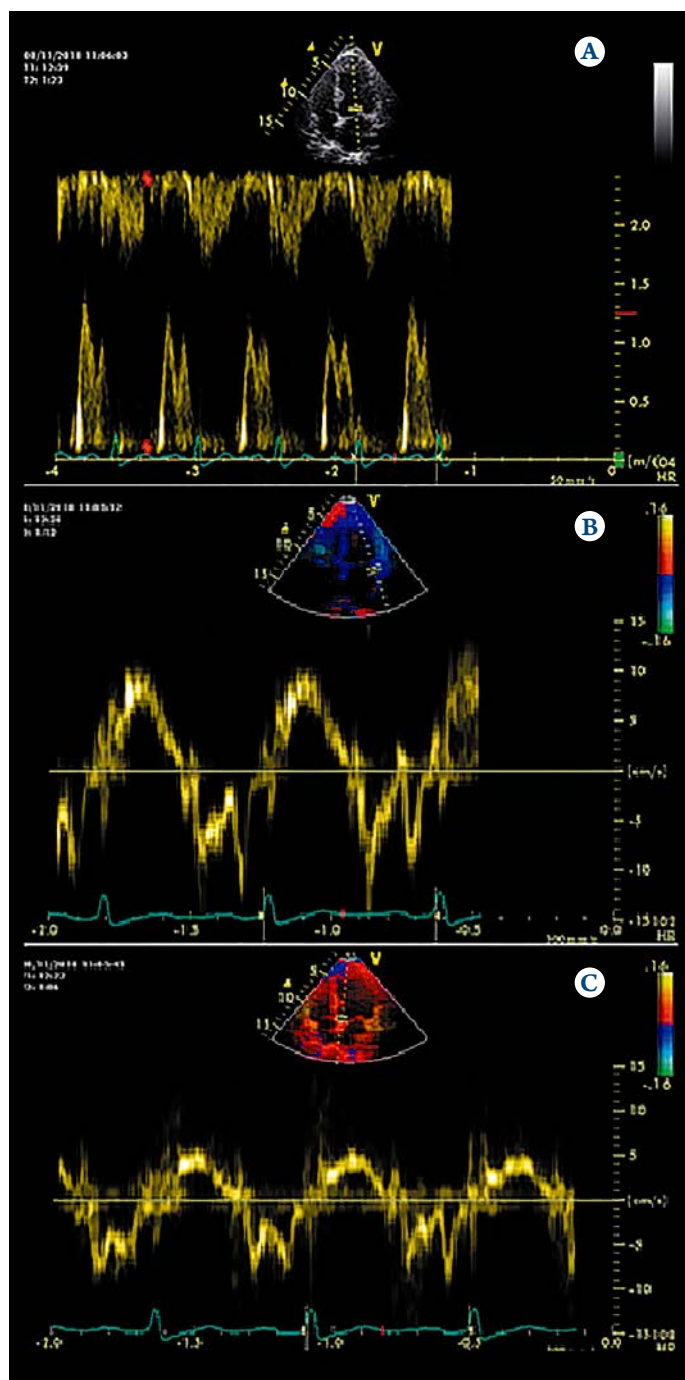
Thus, only 8 (10.0%) of 80 patients did not present the common causes of dyspnea (see Figure 2).

Discussion

Based on our study of the 67.1% of patients referred to ESE for chest pain, heart rhythm disorders, or preventive examination, a standard conclusion is sufficient to determine the indications for invasive coronary angiography and for a decision to be made with regard to myocardial revascularization [18]. However, in 32.9% of patients who complained of dyspnea, the result of the standard ESE with the regional myocardial contractility assessment does not allow the nature of dyspnea to be identified. Despite high pretest probability of identifying CAD in patients with dyspnea [19], we found that a relatively small number of these patients (17.5%) had positive ischemic test results. This was consistent with the findings of Argulian et al. [7], and the rate of positive tests in patients with and without dyspnea did not differ significantly.

It seems to be clear that when using the standard ESE protocol in the study subjects, it can be concluded that 17.5% of patients had dyspnea of ischemic nature, which required either myocardial revascularization or

Figure 4. Echocardiogram of a 59 year-old female patient with coronary artery disease, dyspnea, history of revascularizations



A – E and A peaks of transmitral blood flow with exercise in the pulsed-wave Doppler mode; B, C – septal and lateral mitral annular diastolic velocities with exercise in the tissue Doppler mode.

an adequate anti-ischemic therapy. The cause of dyspnea was unknown in the remaining 82.5% of patients. Using an additional advanced ESE protocol in 72.5% of patients, we were able to estimate the causes of dyspnea and provide information about a possible further diagnosis and treatment algorithm. Thus, advanced ESE provided valuable diagnostic information in 90.0% of patients with dyspnea.

In some patients with negative ischemic and diastolic stress tests and without other objective causes of dyspnea, the advanced ESE protocol allowed for a conclusion of a more likely extracardiac cause of dyspnea, and the patient's possible deconditioning. It should be noted that the advanced ESE technique, including the Doppler analysis, has already been included in the 2020 guidelines of the American Society of Echocardiography [20]. There is little data on diastolic stress tests and advanced ESE protocols in the Russian literature, and there is no original research. The review by Dzhioeva et al. [21] is of particular interest, since it investigate the possibilities of the diastolic stress test in the risk stratification in patients before non-cardiosurgery interventions.

Our study was limited by the fact that alternative objectification methods were used for different dyspnea patterns and diastolic ESE results. For example, it would be useful for a larger study to perform blood tests for CHN markers (NT-proBNP), compare ESE data with cardiorespiratory tests, and evaluations of pulmonary function. Moreover, the advanced ESE protocol in assessing changes of symptoms and objective indicators on the top of heart and bronchopulmonary disease treatment can be of both scientific interest and practical significance.

It should be noted that this ESE protocol does not only have clinical benefits but is also cost-effective. The technique does not require additional financial investments. The diastolic stress test can be performed using the standard modes of any up-to-date ultrasound device. This technique also makes it possible for conclusions to be drawn not only from the echocardiographic findings at rest and

with exercise, but also from the clinical interpretation of complaints made by patients during the test. In the CHF diagnosis and treatment guidelines, the alternative methods for CHF diagnosis with preserved LVED include laboratory tests for BNP and NT-proBNP. This is also possible using cardiorespiratory stress testing, but this technique is more expensive and requires additional gas analysis equipment.

Thus, our study showed the possibility of using the ESE protocol with clinical evaluation of dyspnea patterns and echocardiographic evaluation of LV diastolic performance in the differential diagnosis of dyspnea.

Conclusions

1. Dyspnea is a more frequent cause of exercise-stress echocardiography than typical exertional angina pectoris. Only 17.5% of patients have dyspnea of ischemic origin.
2. Chronic heart failure with preserved left ventricular ejection fraction, hypertensive reaction to load, chronotropic incompetence, and bronchopulmonary pathology are common causes of non-ischemic dyspnea.
3. The advanced exercise-stress echocardiography protocol with estimation of E/e' , dPTR assessment, specifying the clinical features of dyspnea and its possible origin, provides valuable clinical information regarding further diagnostic and treatment algorithm in most patients with non-ischemic dyspnea.

No conflict of interest is reported.

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