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Hypertensive response to exercise: prevalence and impact on stress echocardiography results

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Abstract

Background. Hypertensive response of blood pressure (BP) to exercise has substantial prognostic impact. Hypertensive response to exercise is shown to be a predictor for development of hypertension and stroke. The data concerning hypertensive response to exercise influence on stress echocardiography results are controversial. **Objective.** The aim of the study was to assess the frequency of hypertensive response of BP to exercise and its impact on the result of the stress echocardiography on treadmill in patients with known or suspected ischemic heart disease. **Design and methods.** We analyzed 3434 tests performed in out-patient department during 1 month period (21.01–21.02) of every year since 2007 to 2020. We studied the occurrence of hypertensive response to exercise during exercise stress echocardiography on treadmill and its relation to positive results of the test. **Results.** The prevalence of hypertensive response to exercise varied from 8,6 % to 41,5 % (average in 14-year period — 23,24 %), however, the proportion of tests with hypertensive response to exercise significantly declined in the period from 2015 to 2020 years. Patients with hypertensive response to exercise showed significantly more frequent positive tests in comparison to patients with normotensive BP response: 40,6 % vs 31,0 % (r = 12,2, p = 0,0005), though yearly analysis showed no correlation between the number of tests with hypertensive response to exercise and number of positive tests (r = 0,21; p = 0,47). **Conclusions.** Significant correlation between BP response and stress echocardiography results means that hypertensive response to exercise has an impact on the test results, therefore antihypertensive treatment optimization is essential before test.

Key words: stress-echocardiography, hypertension, hypertensive response to exercise

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Гипертензивная реакция на нагрузку: распространенность и влияние на результаты стресс-эхокардиографии

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Резюме

Актуальность. Гипертензивная реакция артериального давления (АД) на нагрузку (ГРН) имеет существенное прогностическое значение, являясь предиктором развития у пациента гипертонической болезни и церебральных сосудистых событий. Литературные данные о влиянии ГРН на результаты стресс-эхокардиографии (стресс-ЭхоКГ) противоречивы. **Цель исследования** — оценить частоту возникновения ГРН при проведении стресс-ЭхоКГ на тредмиле у пациентов с известной ишемической болезнью сердца или подозрением на нее и влияние ГРН на результаты исследования. **Материалы и методы.** Были проанализированы результаты 3434 стресс-ЭхоКГ тестов, выполненных в амбулаторном порядке в течение периода 1 месяца (21.01–21.02) каждого года за период с 2007 до 2020 годы. Были изучены частота возникновения ГРН в ходе стресс-ЭхоКГ исследования и взаимосвязь гипертензивной реакции с положительным результатом исследования. **Результаты.** Распространенность ГРН у пациентов, которым была выполнена стресс-ЭхоКГ в разные годы, составила от 8,6 % до 41,5 % (в среднем за 14 лет — 23,2 %), при этом в период с 2015 по 2020 годы доля тестов с ГРН снизилась. Среди пациентов с ГРН положительный тест встречался чаще, чем среди пациентов с адекватной реакцией АД: 40,6 % против 31,0 % (r = 12,2, p = 0,0005). **Выводы.** Наличие взаимосвязи между реакцией АД на нагрузку и результатами стресс-ЭхоКГ говорит о влиянии ГРН на результаты исследования и необходимости тщательного подбора антигипертензивной терапии перед исследованием.

Ключевые слова: стресс-эхокардиография, артериальная гипертензия, гипертензивная реакция на нагрузку

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Introduction

Arterial hypertension is wide-spread all over the world — up to 30–45 % of the population has criteria for the disease [1]. The burden of the disease among the Russian Federation population is 72.1 % when using the ACC/AHA 2017 criteria for hypertension according to the big national registry [2]. The comprehensive investigation in patients with hypertension has crucial socio-economic value. The initial evaluation of hypertensive patients includes serial blood pressure (BP) measurements at home and in the office with the addition of ambulatory blood pressure monitoring if needed. Fundoscopy, microalbuminuria analysis and echocardiography are obligatory in these patients [3].

Exercise stress-tests are not commonly used in routine workup in hypertensive patients. Moreover, according to ESC Guidelines for the management of arterial hypertension stress-tests are not recommended for diagnosis of the disease due to some restrictions [4]. Nevertheless, literature data shows the prognostic value of the hypertensive response of blood pressure to exercise (HRE). L. Holmqvist et al (2012) report that HRE can serve as a predictor for the development of hypertension in the future irrespective of blood pressure at rest [5].

The most common criteria for HRE are the BP levels from the Framingham study with the largest selection of patients — 1978. The authors suggest treating as HRE the elevation of systolic BP ≥ 210 in men and ≥ 190 in women during Bruce protocol on a treadmill [6]. Some patients demonstrate the early BP rise and low to medium tolerance to exertion, therefore S. Weiss et al. (2010) offered the threshold ≥ 180/90 mmHg from the second stage of Bruce protocol on a treadmill as the criterion for HRE in these patients [7]. It was noticed that BP during stress-test on the bicycle can be higher than on a treadmill in the same patient [8, 9], that's why separate criteria for HRE for this type of exertion were introduced — the systolic BP rise ≥ 220 mmHg in men and ≥ 200 mmHg in women [10]. Taking into consideration that some patients have high BP before the test T. G. Allison et al. (1999) determine HRE as systolic BP increment ≥ 60 mmHg in men and ≥ 50 mmHg in women from baseline BP [11]. Systolic BP rise ≥ 182 mmHg and diastolic BP ≥ 96 mmHg are the accepted criteria for HRE during pharmacological stress-echocardiography with dobutamine [12].

There is consent among most authors that HRE is a predictor for future hypertension development in non-hypertensive patients [13–17]. R. Mizuno et al. (2016) demonstrated that patients with HRE have higher myocardial mass in comparison to patients with normal BP response [18]. Endothelial dysfunction plays a significant role in the mechanism of HRE and serves as a separate negative prognostic marker [19].

Beyond the connection to the natural history of hypertension, HRE is associated with increased cardiovascular risk [20]. For example, patients with HRE have a higher prevalence of carotid artery atherosclerosis on ultrasound [21] and more frequent ischemic stroke [22]. Moreover, O. Prada-Delgado et al. (2015) demonstrated that stress-induced left ventricle systolic dysfunction in patients with HRE and no coronary artery lesions is an independent predictor for cardiovascular events [23].

The purpose of the study — to investigate the frequency of HRE during stress echocardiography on a treadmill in patients with known or suspected coronary artery disease (CAD) and to assess the influence of BP response on the test results.

Material and methods

We analyzed the frequency of HRE in out-patients, directed to exercise stress echocardiography in NMRC n.a. VA Almazov during one month of every year from 2007 to 2020 years. The standard interval for analysis began from January 21st to February 21st of every year, since this interval is stable in the number of working days and contains no public holidays. Stress echocardiography was performed on treadmill T-2100 (GE Healthcare, USA), the images were recorded into the GE Vivid 7 equipment (GE Healthcare, USA). In most patients, the standard Bruce protocol was used with manual BP control on the left arm at rest, on every stage of exertion and in the recovery period. All tests were divided into two groups depending on BP response according to the aforementioned Framingham and Weiss criteria for HRE on a treadmill [6,7].

Statistical analysis

The data are partially presented as mean ± standard deviation, partially — as absolute numbers and proportions of patients with different test results and types of BP response to exercise. The difference between groups in the frequency of the investigated parameter was assessed using cross-tables with $\chi 2$ criterion. The linear relation between two quantitative parameters was assessed with the Pearson correlation coefficient. Statistical analysis was performed with the Statistica 7.0 software (StatSoft, Inc., USA).

Results

The general number of analyzed tests was 3434.

The number of out-patient tests in NMRC n.a. VA Almazov increased gradually from 2007 till 2012 reaching the plateau from 2012 year with the average number of tests in a month 294.4 ± 35.4. The number of tests with HRE increased proportionally (fig. 1), reaching its peak in 2015 year (41.5%). During the period from 2015 to 2020 the proportion of tests with HRE declined: 2016–24.8% ($\chi 2$ = 9.73; p= 0.0018); 2017–29.1% ($\chi 2$ = 4.15; p= 0.0417); 2018–28.6%

Figure 1. Total number of out-patient tests and number of tests with hypertensive response per month in 2007-2020

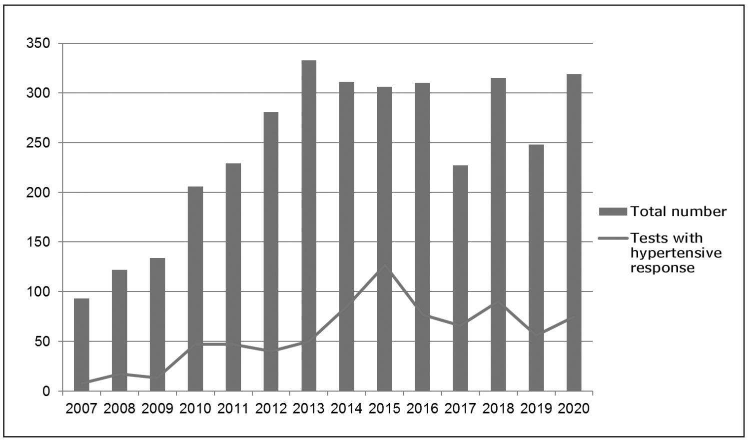
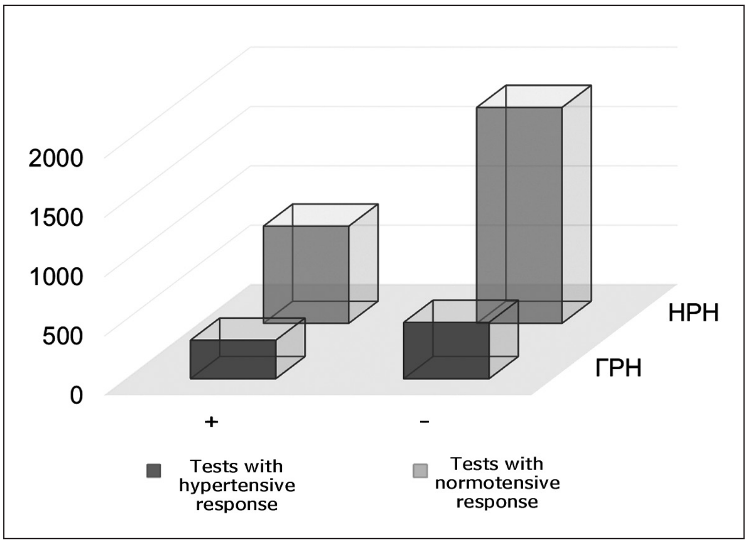
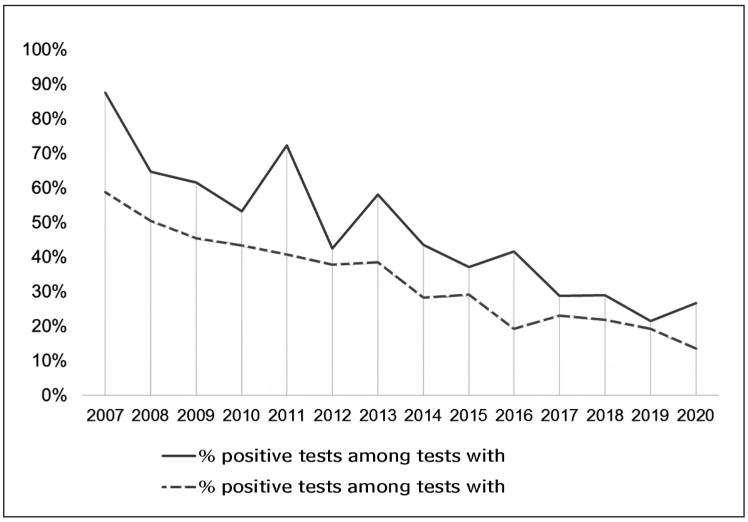


Figure 2. Total number of positive tests with hypertensive and normotensive response in 2007–2020



Note: "+" — positive stress-echocardiography; "–" — negative stress-echocardiography.

Figure 3. The ratio of positive tests among tests with hypertensive and normotensive response per month in 2007–2020



Table

TOTAL NUMBER OF POSITIVE AND NEGATIVE TESTS WITH HYPERTENSIVE AND NORMOTENSIVE BLOOD PRESSURE RESPONSE TO EXERCISE

Year	Number of tests	Number and ratio (%) of tests with hypertensive response to exercise	Number and ratio (%) of positive tests	χ^2*	p-level
2007	93	8 (8.6%)	57 (31.29%)	2.53	0.1114
2008	122	17 (13.93%)	64 (52.46%)	1.19	0.2758
2009	134	13 (9.7%)	68 (64.18%)	1.22	0.2696
2010	206	47 (22.82%)	94 (45.63%)	1.4	0.2362
2011	229	47 (20.52%)	108 (47.16%)	15.05	0.0001
2012	281	40 (14.23%)	108 (38.43%)	0.33	0.5681
2013	333	50 (15.02%)	138 (41.44%)	6.65	0.0099
2014	311	85 (27.33%)	101 (32.48%)	6.52	0.0107
2015	306	127 (41.5%)	99 (32.35%)	2.15	0.1426
2016	310	77 (24.84%)	96 (30.97%)	15.34	0.0001
2017	227	66 (29.07%)	56 (24.67%)	0.85	0.3568
2018	315	90 (28.57%)	75 (23.81%)	1.79	0.1807
2019	248	56 (22.58%)	49 (19.76%)	0.13	0.7212
2020	319	75 (23.51%)	53 (16.61%)	7.15	0.0075
All period	**3434**	**798 (23.24%)**	**1166 (33.95%)**	**25.27**	**< 0.00001**

Note: * — when comparing number of positive tests in patients with hypertensive and normotensive response to exercise.

($\chi 2$ = 5.51; p = 0.018); 2019–22.6% ($\chi 2$ = 11.39, p = 0.0007); 2020–23.5% ($\chi 2$ = 11.84; p = 0.0006). Also, the relation between general number of tests and number of tests with HRE yearly was observed (r = 0.8; p = 0.001).

Among 3434 stress echocardiography studies in 14 years, 1166 were positive (33.95%). Upon that patient with HRE had significantly higher prevalence of positive result comparing to patients with normal BP response: 40.6% vs. 31.03% ($\chi 2$ = 12.2; p = 0.0005) (fig. 2). In all years with no exclusion, the percentage of positive tests among patients with HRE was higher than the percentage of positive tests among patients without HRE, though these differences were significant (p < 0.05) only in a distinct year (table, fig. 3).

Discussion

The HRE during exercise stress echocardiography was observed in a large proportion of patients — in every fourth on average. This could be explained by the mode of selection of patients — most of them had known or suspected CAD combined with hypertension.

The mechanism of HRE as a pathologic phenomenon is complicated. R.H. Fagard et al. (1996) report the absence of an adequate reduction in peripheral vascular resistance in response to exercise in these patients [24]. G. Thanassoulis et al. (2012) state that HRE has combined mechanism with the two main components — the increased arterial wall stiffness and endothelial dysfunction, the first being more pronounced in elderly, the second in the opposite — in younger patients [25]. Among biochemical mechanisms of HRE the angiotensin II elevation on exertion theory is proposed in the literature [26], the decrease in endothelial NO production during exercise which leads to vasodilation reserve reduction is also discussed [27]. S.Y. Jae et al. (2006) suggest that HRE is associated with inflammation markers increase, particularly leukocytosis [28].

One of the most common explanations for left ventricular systolic dysfunction in response to HRE is global subendocardial ischemia uprise due to tissue oxygen consumption and supply mismatch with the double production increase (systolic BP X heart rate). Besides, it was shown that left ventricle hypertrophy leads to coronary arteries vasodilation reserve reduction, which in its turn is reflected in pathologic increase in microcirculation peripheral vascular resistance, causing the global subendocardial ischemia in HRE.

Despite the unclear clinical value of HRE, there are many published studies, devoted to the prognostic implications of this phenomenon. On the opposite, there are just a pair of publications of one group of authors, who witness against such a prognostic significance of HRE [29, 30].

The increased after-load negative influence on left ventricular systolic function was shown in experimental [31] and clinical studies [32], moreover the degree of HRE (both systolic and diastolic BP increment) may have a negative correlation with the specificity of stress echocardiography.

In the P. Mottram et al. study (2004) 41 patients with HRE had lower longitudinal strain and strain rate in TDI modality and lower cyclic variability of integrated backscatter during stress echocardiography in comparison to 17 patients with normal BP response, moreover, HRE was associated with subclinical left ventricular systolic dysfunction irrespective of hypertension at rest, left ventricle hypertrophy and significant diastolic dysfunction [33]. J. H. Shin et al. (2003) report that wall motion abnormalities in response to HRE are more frequent in women [34].

T. L. Jurrens et al. (2012) provide the opposite point of view. In two groups with HRE and normal BP response, the authors found no difference in false-positive results of stress echocardiography among 508 patients with performed stress echocardiography and coronary angiography [35]. S. Abram et al. (2017) concluded that the incidence of coronary artery stenosis ≥ 50 % in patients with HRE and normal BP response during the dobutamine stress echocardiography is the same, while the incidence of coronary artery stenosis ≥70 % is higher in the HRE group [36].

Thereafter the HRE influence on left ventricular systolic function parameters is evident and valid, though the question of management of patients with isolated HRE is not clarified in current guidelines. At the moment it can be said without a doubt that patients with HRE and uncontrolled hypertension at rest require therapy enhancement according to current ESC Guidelines on the management of arterial hypertension. At the same time, it should be taken into consideration that despite the absence of direct recommendation to treat the isolated HRE the studies demonstrated a negative prognostic effect of this phenomenon.

According to our data, the number of tests with HRE increased in proportion with the general number of tests and reached its peak in 2015 (41.5 % among all tests), while the proportion of tests with HRE declined from 2015 to 2020. This can be explained by the more effective hypertension and CAD management in recent years.

In our study, the incidence of positive tests appeared to be significantly higher in comparison to patients with normal BP response during the whole period and every single year.

Basing on that it can be suggested that patients with HRE have a higher prevalence of obstructive CAD or that transient wall motion abnormalities could be explained by the HRE itself even in the absence of significant coronary artery stenosis. Both these hypotheses are supported in the literature. Truly, many authors witness that patients with HRE possess a worse cardiovascular risk profile and more pronounced target organ damage. Also, there are some studies, illustrating the possibility of transient wall motion abnormalities in a patient with HRE even in the absence of CAD [30]. Therefore, based on our data the HRE has a direct influence on the stress echocardiography results.

According to ASE guidelines on performance of stress echocardiography, patients with HRE and positive results of the test should be managed in the same way as all the other patients with positive tests [37]. On one hand, the authors refer to the aforementioned study by J. Ha et al. (2002) and confess the hypothesis that stress-induced wall motion abnormalities in patients with HRE are less specific in coronary artery stenosis detection [32]. On the other hand, the study by A. M. From et al (2010) showed that patients with HRE on the opposite don't have an increased probability of positive results, and this proportion of patients with positive tests revealed CAD on coronary angiography [38]. It should be mentioned the weakness of this study, which was single-center and only 20 % of patients with positive stress echocardiography results underwent coronary angiography.

Thereafter, the big data in our study, gathered from many years demonstrate the significant influence of BP response to exercise during stress echocardiography on test results, which correspond to the literature data and can have an impact on long-term prognosis in this group of patients.

Conclusion

1. The prevalence of HRE during stress echocardiography varied in different years from 8.6 % to 41.5 % (23.2 % on average), meanwhile, the decline of the proportion of tests with HRE in the period of 2015–2020 suggests more effective medical treatment in patients with known or suspected CAD.

2. The HRE influence on stress echocardiography results in detecting CAD supports the demand for more effective medical therapy for hypertension adjustment before the test.

Conflict of interest
The authors declare no conflict of interest.

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