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Blood pressure response: impact on the results of ABCDE-stress echocardiography in patients with known and suspected coronary artery disease

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Abstract

Aim: To assess the incidence and predictors of hypertensive response to exercise (HRE) of blood pressure during stress echocardiography (SE) with physical exercise in patients with known or probable coronary artery disease, and the effect of HRE on the results of the five-step SE.

Methods: The single-center study included 193 patients who underwent ABCDE-SE. The incidence of HRE, predictors of its occurrence, and the relationship with positive results of the study protocol steps were investigated.

Results: HRE was detected in 36.3% of patients (70 patients) and occurred more frequently during the bicycle ergometer test ($p = 0.027$). Patients with HRE had a significantly lower peak wall motion score index ($p = 0.050$) and achieved a preload ratio ($p = 0.035$), as well as higher left anterior descending coronary artery (LAD) blood flow velocity at rest and during exercise ($p = 0.009$ and $p = 0.008$, respectively). They also showed higher peak left ventricular (LV) contractile reserve and force ($p = 0.002$ and $p = 0.006$). Reduced contractile reserve was less common in patients with HRE ($p = 0.013$). Predictors related to HRE development were identified: history of LAD stenting, thickness of the LV posterior wall, LAD blood flow velocity, and normal LV force at rest ($p = 0.006$, $p = 0.022$, $p = 0.004$, and $p = 0.003$, respectively), as well as a positive step C ($p = 0.005$).

Conclusions: The prevalence of HRE, its predictors, and the relationship with the ABCDE-SE results were revealed. The correlation between blood pressure response to exercise and SE steps, as well as its prognostic significance, needs further study.

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Keywords

ABCDE-stress echocardiography, hypertensive response to exercise, coronary artery disease

Introduction

Contemporary functional stress echocardiography (SE) testing involves more than just wall motion responses during stress. ABCDE-SE provides a representation of five functional reserves: epicardial blood flow (A—Asynergy), diastolic (B—B-lines), contractile [C—left ventricular contractile reserve (LVCR)], coronary microcirculatory (D—Doppler coronary flow velocity reserve), and chronotropic reserves [E—electrocardiogram (ECG)-heart rate reserve] [1].

Along with the new parameters of stress testing, conventional indices—such as the assessment of ECG dynamics, exercise tolerance, and blood pressure (BP) response to exercise—remain relevant as well.

BP increase during exercise is a physiological response to the increased oxygen consumption of muscles and tissues. The degree of BP increase is determined by the balance between an increase in cardiac output and a decrease in total peripheral vascular resistance [2, 3]. An exaggerated increase in BP—hypertensive response to exercise (HRE)—is considered a pathological phenomenon. BP responses to exercise have prognostic significance for future hypertension, target organ damage, and death [4]. Therefore, the adequacy of antihypertensive treatment should be evaluated in terms of normalization of stress-related BP responses [5–7]. The incidence of HRE in the healthy population varies from 3–4% to 18% across studies [8], while among patients with masked arterial hypertension, HRE occurs in 40–58% of cases [9].

The phenomenon of LV hypercontractility, or the "hypercontractile phenotype"—characterized, among other features, by systolic hypertension and increased oxygen consumption due to significantly elevated contractile force—appears to be closely related pathophysiologically to HRE [10–12].

Currently, there is insufficient information on BP response during the widely used ABCDE-SE in patients with known or suspected coronary artery disease (CAD), its predictors, and its impact on protocol results and long-term prognosis.

Thus, given the high prevalence of HRE and its prognostic and practical significance, it is reasonable to analyze the incidence of HRE in outpatients and inpatients with suspected or known CAD and varying degrees of comorbidity, to identify the correlation between BP response to exercise and LV contractility index, and to examine the relationship between exaggerated BP elevation during exercise and the results of a contemporary SE protocol.

Materials and methods

A total of 193 consecutive patients aged over 18 years with complaints of chest pain and/or dyspnoea with a high and moderate (with other cardiovascular risk factors) pre-test probability of CAD were included in the single-centre study. The inclusion criteria were: ability to perform exercises within the context of SE, no severe valvular disease, no significant arrhythmia, and no significant concomitant pathology limiting life expectancy. All patients received therapy in accordance with the prescriptions corresponding to the established diagnosis. All patients included in the study underwent a standard general clinical examination (history taking, physical examination, ECG); laboratory tests (complete and biochemical blood counts, troponin and NT-proBNP levels if medically required); standard echocardiographic examination; coronary angiography if medically required; and ABCDE-SE [1, 13].

Exercises were performed on a Schiller MTM-1500 Med TM (Switzerland) or Schiller Ergosana ERG 911S/LS horizontal ergometer bicycle (Switzerland). Ultrasound images were recorded and analysed during cardiac, pulmonary, and coronary scans using an expert-class Vivid E90 (GE Healthcare, USA) with a 3.5 MHz M5S sector phased array transducer (GE Healthcare, USA); presets were used to visualise coronary arteries. All steps were performed by the same expert. The majority of patients underwent the treadmill

(TM) test according to the standard Bruce protocol (intensity categorized as: Low: < 5 METs; Moderate: 5–8 METs; High: > 8–10 METs; Very High: > 10 METs) [14], while ergometer bicycle (EB) tests used a 50–25–25 protocol (Low: < 50 W; Moderate: 50–100 W; High: 100–175 W; Very High: > 175 W) [15]. Systolic and diastolic BP were measured using an automatic BP monitor on the right arm at rest, each stress step, and during recovery.

The five-step SE protocol represented the sequential assessment of the following parameters at rest and at peak stress: regional wall motion abnormality (RWMA) and wall motion score index (WMSI) using a 4-point scale in a 16-segment model of the LV at step A; total B-lines by pulmonary ultrasound scan at 4 points, from the mid-axillary to the mid-clavicular line in the third intercostal space at step B; contractile reserve as a ratio of LV force during stress to LV force at rest (the ratio of systolic BP to end-systolic LV volume was taken as LV force) at step C; coronary reserve at step D by coronary flow of the distal part of the left anterior descending coronary artery (LAD) visualised in doppler from a modified inferior parasternal long-axis position and/or a modified apical 2-, 3-, or 4-chamber position; chronotropic reserve, the ratio of HR during exercise to HR at rest, at step E.

Criterion A was considered positive in case of induced RWMA, in other words, when WMSI at rest was increased (threshold value ΔWMSI ≥ 0.12), which corresponded to a 1-point deterioration in at least 2 of 16 segments or a 2-point deterioration in 1 segment. Step B was considered positive when ≥ 2 B-lines increased; step C, when the value was < 2.0; step D, when the increase in blood flow velocity in the LAD under stress was less than 2.0 times; step E, when the increase in HR was < 1.80. Each positive step in the study result was assigned 1 point (0 points if all steps were negative; 5 points if all steps were positive) [1, 13].

Patients were divided into phenotypes based on LV force at rest and at peak stress: subnormal force with LV force value less than 3.24 mmHg/mL (less than 25th percentile); normal force, from 3.24 to 5.48 mmHg/mL (more than 25th percentile and less than 75th percentile); supernormal force, more than 5.48 mmHg/mL (more than 75th percentile); hypercontractile phenotype (force value > 8 mmHg/mL) was allocated separately [11].

The criteria for HRE in exercise testing are not standardized and vary among different authors and depending on the type of stress. Thus, an increase in systolic blood pressure (SBP) during TM HRE is considered to be ≥ 190 mmHg in women and ≥ 210 mmHg in men [16] or an increase in SBP ≥ 180 mmHg from the second step of the test [5]. It is noted that BP levels during EB exercises may be higher in the same patient than during the TM test [17, 18]. Therefore, different HRE criteria were established for EB tests, namely SBP elevation during exercise in men ≥ 220 mmHg and in women ≥ 200 mmHg [19]. Taking into account that some patients have high BP immediately at the beginning of exercise, Allison TG et al. [7] defined HRE as the elevation of SBP compared to baseline in men ≥ 60 mmHg and in women ≥ 50 mmHg. Thus, all studies were divided into normotonic response to exercise (NRE) and HRE tests according to the aforementioned criteria [5, 7, 16–19].

For statistical data processing, SPSS software (version 27.0) was used. The sample size was estimated according to the method of Otdel'nova KA [20] (given power of the study 80%; significance level 0.05). Quantitative variables were described as the arithmetic mean (M) and standard deviation of the mean (SD) (for normal distribution) or as the median (Me) and interquartile range (IQR) (for asymmetric distribution). Distributions were tested using the Kolmogorov-Smirnov test. Qualitative variables were described by absolute (n) and relative (%) values.

The significance of differences between groups in quantitative variables was assessed using the Mann-Whitney U test/Kruskal-Wallis test. For qualitative variables, the Pearson chi-square (χ^2)/Fisher's exact test was used, depending on the minimum expected number. A p-value < 0.05 was considered significant. The direction and strength of the correlation between the indicators were assessed using the Spearman correlation coefficient (nonparametric correlation analysis). The dependence of the binary indicator on quantitative or categorical indicators was identified using data from single- and multivariate binary logistic regression with determination of the odds ratio (OR) and 95% confidence interval (95% CI).

Results

More than half of the studied group were men (*n* = 111, 57.5%), with an average age of 61.8 ± 10.1 years. Most patients had comorbidities and/or additional risk factors. The most common conditions were hypertension (90.2%), ischemic heart disease (59.6%), and dyslipidemia (77.2%). All patients received therapy according to their established diagnoses and existing recommendations. The main drug groups included beta blockers (62.7%), angiotensin-converting enzyme inhibitors (47.2%), angiotensin receptor blockers (28.0%), calcium channel blockers (30.1%), and diuretics (22.8%). Arterial hypertension was stable and controlled in all studied patients. Clinical and laboratory characteristics are presented in Tables 1 and 2.

Table 1. Clinical and demographic characteristics of the study population

Index	Results
Obesity, *n* (%)	69 (35.8)
Overweight, *n* (%)	77 (39.9)
Current and past smoking, *n* (%)	36 (18.7)
Hypertension history, *n* (%)	174 (90.2)
CAD history, *n* (%)	117 (60.6)
STEMI history, *n* (%)	35 (18.1)
non-STEMI history, *n* (%)	25 (13.0)
Type 1 diabetes mellitus, *n* (%)	3 (1.6)
Type 2 diabetes mellitus, *n* (%)	48 (24.9)
Atrial fibrillation history, *n* (%)	19 (9.8)
PE, *n* (%)	2 (1.0)
Peripheral artery disease, *n* (%)	11 (5.7)
ACVE history, *n* (%)	10 (5.2)
CKD C1, *n* (%)	6 (3.1)
CKD C2, *n* (%)	12 (6.2)
CKD C3, *n* (%)	3 (1.6)
COPD, non-acute, *n* (%)	18 (9.3)
Dyslipidemia, *n* (%)	149 (77.2)
HF 1 class NYHA, *n* (%)	8 (4.1)
HF 2 class NYHA, *n* (%)	26 (13.5)
SCORE risk (M ± SD)	4.4 ± 4.1
CAG, *n* (%)	108 (56.0)
No CA lesion according to CAG data, *n* (%)	22 (11.4)
single-vessel CA disease, *n* (%)	23 (11.9)
multivessel CA disease, *n* (%)	63 (32.6)
ECG sinus rhythm, *n* (%)	192 (99.5)
LBBB, *n* (%)	6 (3.1)
AV block 1-st degree, *n* (%)	6 (3.1)
Non-specific ST segment depression, *n* (%)	4 (2.1)

ACVE: acute cerebrovascular events; AV: atrioventricular; CA: coronary artery; CAD: coronary artery disease; CAG: coronary angiography; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; HF: heart failure; LBBB: left bundle branch block; non-STEMI: non-ST-segment Elevation Myocardial Infarction; NYHA: New York Heart Association; PE: pulmonary embolism; SCORE: Systematic COronary Risk Evaluation; STEMI: ST-segment Elevation Myocardial Infarction

Table 2. Laboratory test parameters

Index	Results
TC, mmol/L (M ± SD)	4.8 ± 1.6
LDL, mmol/L (M ± SD)	2.9 ± 1.2

Table 2. Laboratory test parameters (*continued*)

Index	Results
HDL, mmol/L (M ± SD)	1.3 ± 0.4
TG, mmol/L (M ± SD)	1.8 ± 1.3
Glucose, g/L [Me (IQR)]	4.7 ± 0.5
Glycated hemoglobin, % (M ± SD)	7.3 ± 2.5
GFR (CKD-EPI), mL/min/1.73 m^2 [Me (IQR)]	74.5 (63.1; 86.8)
Creatinine, mmol/L [Me (IQR)]	87 (76; 98)
NT-proBNP, pg/mL (M ± SD)	183.4 ± 426.2
CRP, mg/L (M ± SD)	5.6 ± 9.9

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CRP: C-reactive protein; GFR: glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NT-proBNP: N-terminal pro-B-type natriuretic peptide; TC: total cholesterol; TG: triglycerides

LV ejection fraction at rest was more than 50% in 90.7% of patients. SE revealed induced ischemia in 17.6%, subclinical pulmonary congestion in 14.5%, decreased contractile reserve in 74.6%, decreased coronary reserve in 45.6%, and decreased chronotropic reserve in 43.0% of patients. The maximum number of points was 5 (1.6%), with the most common score being 2 (34.2%). Results of the five-step SE are presented in Table 3 and Figure 1.

Table 3. Stress echocardiography findings using the ABCDE protocol

Index	Results
Exercise type, *n* (%)	
EB	138 (71.5)
TM	55 (28.5)
LVEF rest, % [Me (IQR)]	57.6 (54.0; 61.5)
LVEF stress, % [Me (IQR)]	61 (55; 66)
LVMI, g/m^2 (M ± SD)	89 ± 23
RWT, (M ± SD)	0.47 ± 0.1
EDV rest, mL (M ± SD)	81 ± 28
EDV stress, mL (M ± SD)	79 ± 30
WMSI rest (M ± SD)	1.08 ± 0.23
WMSI stress (M ± SD)	1.11 ± 0.25
HR rest, b/min (M ± SD)	76 ± 13
HR stress, b/min (M ± SD)	135 ± 15
SBP/DBP rest, mmHg (M ± SD)	130 ± 14/80 ± 9
SBP/DBP stress, mmHg (M ± SD)	189 ± 24/96 ± 11
Reason for test cancellation, *n* (%)	
Reach of the predefined HR/positive test criteria	107 (55.4)
Fatigue, dyspnoea	52 (26.9)
Other (arterial hypertension, failure, leg pain)	34 (17.6)
Exercise tolerance, *n* (%)	
Low	19 (9.8)
Medium	72 (37.3)
High/very high	84 (43.5)/18 (9.3)
BP response type, *n* (%)	
Normotonic	108 (56.0)
Hypertensive	60 (31.1)
Hypo-/dystonic	15 (7.8)
High initial BP elevation during exercise	10 (5.2)
Total score, *n* (%)	

Table 3. Stress echocardiography findings using the ABCDE protocol (*continued*)

Index	Results
0	19 (9.8)
1	50 (25.9)
2	66 (34.2)
3	40 (20.7)
4	15 (7.8)
5	3 (1.6)

ABCDE: Asynergy, B-lines, Contractile reserve, Doppler coronary flow reserve, and Electrocardiogram parameters; BP: blood pressure; DBP: diastolic blood pressure; EB: ergometer bicycle; EDV: end-diastolic volume; HR: heart rate; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; RWT: left ventricular relative wall thickness; SBP: systolic blood pressure; TM: treadmill; WMSI: wall motion score index

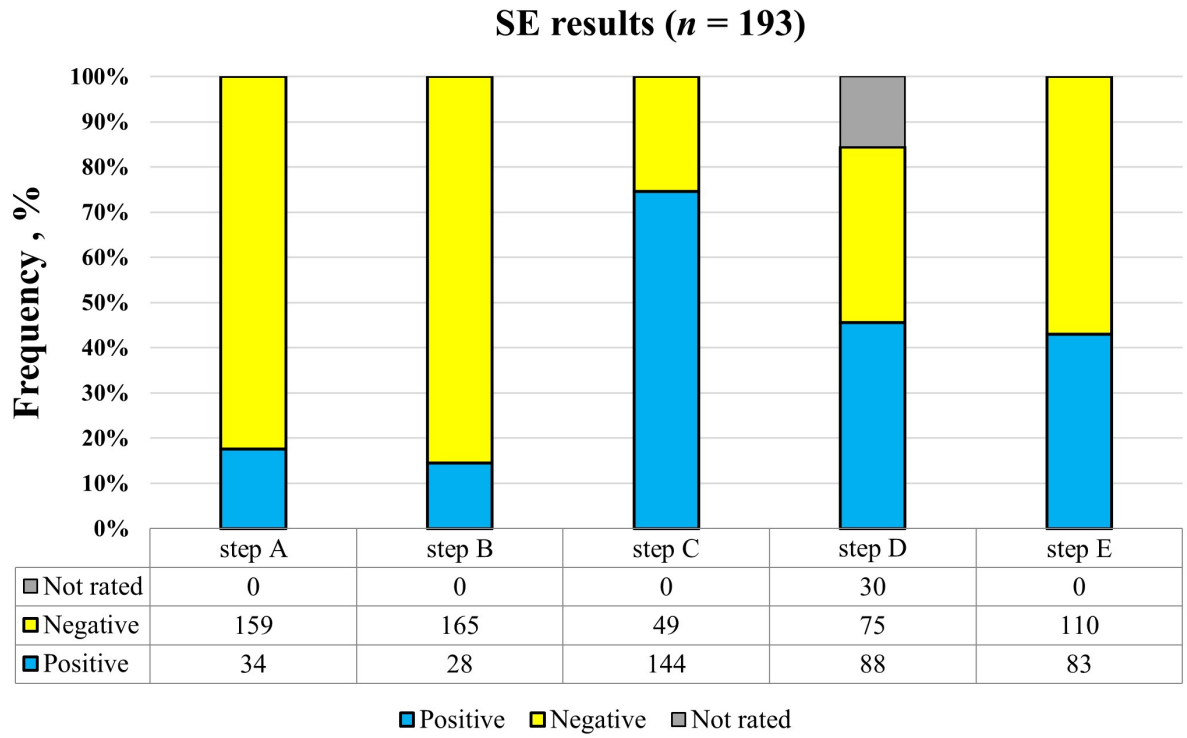


Figure 1. Frequency of positive ABCDE-SE steps in the overall study group. SE: stress echocardiography

We compared the frequency of HRE depending on the type of exercise (Table 4). Patients who underwent exercise on an EB demonstrated HRE more frequently ($p = 0.027$).

Table 4. Comparison of hypertensive response to exercise frequency by exercise type

Exercise type	HRE ($n = 70$)	NRE ($n = 123$)	p
EB ($n = 138$), n (%)	56 (80.0)	82 (66.7)	0.027
TM ($n = 55$), n (%)	14 (20.0)	41 (33.3)	

EB: ergometer bicycle; HRE: hypertensive response to exercise; NRE: normotonic response to exercise; TM: treadmill

We found no statistically significant differences when assessing the influence of coronary disease severity by coronary angiography ($p = 0.191$), the occurrence and clinical variation of CAD ($p = 0.169$), and diabetes mellitus ($p = 0.724$) on the HRE incidence rate.

Due to the lack of differences in HRE incidence depending on comorbidities, the type of BP response was analyzed in the general patient group. Patients with HRE were combined with those having high initial BP increase during exercise for comparison, while patients with NRE were combined with those showing the hypo- and dystonic responses. The HRE group comprised 70 patients, and the NRE group included 123

patients.

When comparing clinical and demographic characteristics, echocardiographic parameters, therapy, and exercise testing results, no statistically significant differences were found for most parameters between the groups. However, patients with HRE showed lower exercise tolerance and higher velocity of the left anterior descending artery (VLAD) both at rest and during stress. The statistically significant differences and trends are presented in Table 5.

Table 5. Characteristics of patients demonstrating hypertensive and normotensive exercise responses

Index	HRE (*n* = 70)	NRE (*n* = 123)	*p*
LAD stent history, *n* (%)	30 (42.9)	55 (44.7)	0.026
HR rest, b/min (M ± SD)	74 ± 14	77 ± 13	0.073
RWT (M ± SD)	0.49 ± 0.10	0.46 ± 0.10	0.070
Thickness of the posterior wall of the left ventricle, mm (M ± SD)	10.6 ± 1.8	10.0 ± 1.7	0.031
Predefined stress achieved, % (M ± SD)	82.5 ± 34.1	93.7 ± 36.5	0.035
Low exercise tolerance, *n* (%)	14 (20.0)	5 (4.1)	0.004
Medium exercise tolerance, *n* (%)	24 (34.3)	46 (37.4)	0.004
High exercise tolerance, *n* (%)	29 (41.4)	55 (44.7)	0.004
Very high exercise tolerance, *n* (%)	3 (4.3)	15 (12.3)	0.003
SBP stress, mmHg (M ± SD)	205 ± 23	180 ± 21	< 0.001
DBP stress, mmHg (M ± SD)	99 ± 9	93 ± 12	< 0.001
SBP response to exercise, mmHg (M ± SD)	76.9 ± 15.3	50.7 ± 18.2	< 0.001
Double product (SBP_{max} × HR_{max}/1,000) (M ± SD)	27.3 ± 4.1	24.8 ± 4.4	< 0.001
WMSI stress (M ± SD)	1.06 ± 0.20	1.13 ± 0.26	0.050
LV force peak, mmHg/mL	8.3 ± 4.2	6.6 ± 3.1	0.006
Normal force rest, *n* (%)	26 (37.1)	23 (18.7)	0.001
Subnormal force peak, *n* (%)	10 (14.3)	38 (30.9)	0.024
Supernormal force peak, *n* (%)	48 (68.6)	74 (60.2)	0.059
Hypercontractile phenotype peak, *n* (%)	27 (38.6)	34 (27.6)	0.034
Contractile reserve (M ± SD)	1.8 ± 0.5	1.6 ± 0.5	0.002
V_{LAD} rest, cm/s (M ± SD)	27.2 ± 8.4	23.7 ± 7.0	0.009
V_{LAD} stress, cm/s (M ± SD)	48.9 ± 16.4	42.6 ± 13.0	0.008

DBP: diastolic blood pressure; HR: heart rate; HRE: hypertensive response to exercise; LAD: left anterior descending coronary artery; LV: left ventricular; NRE: normotonic response to exercise; RWT: relative wall thickness; SBP: systolic blood pressure; V_{LAD}: left anterior descending coronary artery velocity; WMSI: wall motion score index

A comparison was made of the frequency of positive SE protocol steps according to the presence or absence of HRE.

The analysis revealed a statistically significant increase in the frequency of positive step C (reduced contractile reserve) in the HRE group compared to the NRE group (p =0.013). Patients with NRE demonstrated a 2.3-fold higher probability of contractile reserve reduction compared to those with hypertensive stress response.

No statistically significant differences were observed in the frequency of other positive steps within the five-step SE protocol. The comparative frequencies of the positive five-step SE protocol steps stratified by BP response to exercise are presented in Figure 2.

Significant correlations were identified between HRE and the blood flow velocity in the LAD both at rest and during stress, the WMSI at stress, as well as parameters involving BP measurements (Table 6).

Table 6. Association between hypertensive response to exercise and stress echocardiography parameters

Index	R	*p*
Thickness of the posterior wall of the left ventricle	0.159	0.028

Table 6. Association between hypertensive response to exercise and stress echocardiography parameters (*continued*)

Index	R	*p*
LAD stent history	0.245	0.024
V_{LAD} rest	0.186	0.010
V_{LAD} stress	0.177	0.024
SBP stress	0.474	< 0.001
DBP stress	0.259	< 0.001
Double product	0.272	< 0.001
WMSI stress	–0.184	0.011
Exercise tolerance	–0.219	0.002
Achieved % of predetermined exercise tolerance	–0.186	0.010
Contractile reserve	0.261	< 0.001
+Step C	–0.200	0.005
Normal force rest	0.232	0.001
LV force peak	0.216	0.003
Subnormal force peak	–0.162	0.024
Supernormal force peak	0.142	0.048
Hypercontractile phenotype peak	0.144	0.045

DBP: diastolic blood pressure; LAD: left anterior descending coronary artery; LV: left ventricular; SBP: systolic blood pressure; V_{LAD}: left anterior descending coronary artery velocity; WMSI: wall motion score index

Univariate and multivariate regression analyses incorporating significant correlations among clinical, laboratory, anamnestic, and echocardiographic parameters identified predictors of HRE (Table 7). Independent predictors comprised posterior LV wall thickness (p = 0.006), VLAD at rest (p = 0.004), normal resting force (p = 0.003), and positive step C (p = 0.005).

Table 7. Predictors of hypertensive blood pressure response to exercise

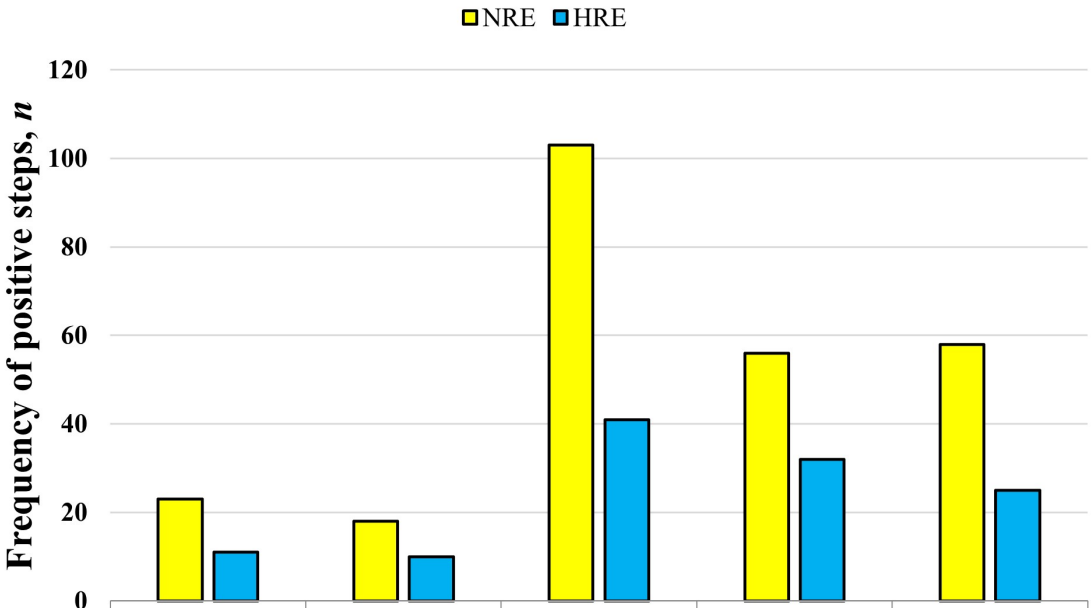
Index	Crude OR, 95% CI	*p*	Adjusted OR, 95% CI	*p*
LAD stent	2.8 (1.1; 7.1)	0.024	7.7 (1.8; 32.7)	0.006
Thickness of the posterior wall of the left ventricle	1.210 (1.019; 1.436)	0.030	1.613 (1.073; 2.426)	0.022
V_{LAD} rest	1.052 (1.008; 1.098)	0.020	1.150 (1.044; 1.266)	0.004
Normal force rest	2.9 (1.5; 5.7)	0.001	13.3 (2.5; 72.3)	0.003
Percentage of exercises predefined by age and gender	0.978 (0.978; 0.997)	0.012		
V_{LAD} peak	1.026 (1.003; 1.049)	0.027		
LV force peak	1.133 (1.040; 1.233)	0.004		
Subnormal force peak	0.418 (0.193; 0.906)	0.024		
Supernormal force peak	1.910 (1.001; 3.645)	0.048		
Hypercontractile phenotype peak	1.894 (1.010; 3.550)	0.045		
Contractile reserve	2.8 (1.5; 5.2)	0.001		
+Step C	0.38 (0.20; 0.74)	0.004	0.07 (0.01; 0.45)	0.005

LAD: left anterior descending coronary artery; LV: left ventricular; V_{LAD}: left anterior descending coronary artery velocity

Discussion

The BP response to exercise demonstrates prognostic significance for the future development of hypertension, target organ damage, and mortality [2, 3, 21]. Consequently, identifying its predictors and evaluating its relationship with cardiac functional reserves may prove valuable not only for elucidating the pathophysiological mechanisms influencing prognosis but also for enhancing prognostic accuracy in individual patients.

In accordance with established criteria, we observed HRE in nearly one-third of patients in our study cohort (n = 70, 36%), consistent with findings from other large-scale investigations. The study by Karev EA et al. [22, 23] analyzed results from 3,434 SE tests performed during outpatient procedures over one-



	step A+	step B+	step C+	step D+	step E+
NRE	23	18	103	56	58
HRE	11	10	41	32	25

Figure 2. Frequency distribution of positive five-step stress echocardiography protocol findings stratified by blood pressure response to exercise. NRE: normotonic response to exercise; HRE: hypertensive response to exercise

month periods (January 21–February 21) annually from 2007 to 2020. The reported prevalence of HRE ranged from 8.6% to 41.5%, with a 14-year average of 23.2% [22, 23]. Our analysis revealed a statistically significant increase in HRE frequency among patients exercising on horizontal bicycle ergometers (p = 0.027), corroborating findings by Balogun MO et al. [17], who demonstrated significantly greater hemodynamic responses during submaximal exercise on bicycle ergometers compared to the TM test.

Patients were stratified into two groups based on BP response: Those exhibiting HRE were grouped with participants demonstrating substantial initial BP elevation during exercise, while normotensive responders were combined with individuals showing hypotonic and dystonic responses. However, this classification may represent a study limitation since exercise-induced BP changes reflect the combined effects of increased cardiac output and reduced total peripheral resistance. Elevated peak SBP may occur both in well-trained individuals performing high-intensity exercise with enhanced cardiac output and in patients with increased arterial stiffness and impaired peripheral vasodilation during exertion, or through a combination of these mechanisms. Consequently, the study population likely exhibits heterogeneity that may account for certain contradictory findings.

Current literature presents conflicting evidence regarding the negative prognostic implications of HRE [6, 24]. While HRE frequently reduces SE specificity and associates with adverse cardiovascular outcomes and elevated SCORE risk [22], its correlation with myocardial ischemia has been established [25, 26]. Marked BP elevation during exercise may increase myocardial oxygen demand, potentially inducing ischemia even without significant coronary artery stenosis [27–29]. Thus, HRE may correlate with heightened cardiovascular event rates independent of cardiorespiratory fitness [30]. Jurrens TL et al. [31] reported more frequent hemodynamically significant CAD among patients with pathological BP elevation during SE, while simultaneously demonstrating that LV regional wall motion abnormalities during HRE may occur without coronary stenosis and carry independent prognostic significance [21]. Although patients without coronary stenoses generally show low long-term myocardial infarction risk [32], subgroups with additional risk predictors (such as transient wall motion abnormalities during SE) can be identified. The relationship between HRE and coronary atherosclerosis remains controversial [31], though patients with confirmed hypertension and multisite atherosclerosis consistently demonstrate higher HRE prevalence than cardiovascularly healthy individuals. Literature also documents increased incidence of cerebral

atherosclerosis, acute cerebrovascular events, LV hypertrophy, and diastolic dysfunction in HRE populations [4, 6].

Paradoxically, some evidence suggests HRE may represent a physiological adaptation through increased cardiac output, potentially conferring a favorable prognosis with reduced ischemia likelihood [33]. Accordingly, HRE might predict the absence of myocardial ischemia [24, 33, 34]. Our data demonstrated a negative correlation between HRE frequency and WMSI, with significantly lower exercise WMSI in HRE patients versus normotensive responders ($p = 0.050$). Additionally, HRE patients exhibited higher LAD flow velocities both at rest and during exercise ($p = 0.009$ and $p = 0.008$, respectively). No significant HRE incidence differences emerged across CAD severity groups ($p = 0.191$), though higher LAD stenting frequency in HRE patients ($p = 0.026$) may explain preserved LV functional reserve, facilitating hypertensive responses.

Exaggerated hypertensive responses frequently necessitate premature test termination, reflected in our HRE cohort's significantly reduced exercise tolerance. However, HRE also correlated with lower mortality and major adverse cardiac event risks, potentially reflecting enhanced LV contractile reserve quantified as force reserve (SBP/end-systolic volume ratio) [33]. This hypothesis aligns with observed intergroup differences in peak LV force, supernormal/hypercontractile phenotype prevalence during exercise, and contractile reserve reduction frequency following the five-step SE protocols.

Karev EA et al.'s analysis [35] of 94 patients without significant coronary disease (confirmed by angiography/MSCT) demonstrated HRE association with elevated LV mass index (100.0 [90.0–107.0] vs 76.0 [68.0–91.0] g/m^2, $p < 0.001$), left atrial volume (36.7 [32.0–46.0] vs 29.7 [26.3–32.0] mL/m^2, $p < 0.001$), SCORE risk (5.0 [2.0–6.0] vs 2.0 [1.0–3.0], $p = 0.004$), comorbid conditions (36.6% vs 12.7%, $\chi^2 = 7.57$, $p = 0.006$), and diastolic dysfunction (39.02% vs 78.18%, $\chi^2 = 15.21$, $p = 0.0001$). Our data similarly revealed significant posterior wall thickness differences ($p = 0.031$) and trending relative wall thickness increases ($p = 0.070$) in HRE patients. Karev's cohort [35] showed HRE correlation with reduced METs (7.4 [5.6–10.0] vs 10.2 [8.4–11.95], $p < 0.001$) and frequent transient wall motion abnormalities (46.34% vs 1.8%, $p < 0.001$), predominantly in lateral/inferior walls—findings paralleling our HRE patients' early test termination due to hypertension. Mazic S et al.'s athlete study [2] ($n = 517$) confirmed that even without structural heart disease, HRE with autonomic dysfunction reduces exercise capacity. Conversely, NRE patients demonstrated higher exercise WMSI than HRE counterparts (1.13 ± 0.26 vs 1.06 ± 0.20, $p = 0.050$), potentially reflecting submaximal stress achievement.

Lauer MS et al.'s prospective study [36] ($n = 594$) found lower severe CAD prevalence in HRE patients (14% vs 25%; OR = 0.51; 95% CI: 0.32–0.81; $p = 0.004$) after adjusting for resting hypertension, age, gender, and fitness. Bouzas-Mosquera C et al.'s retrospective analysis [33] ($n = 10,047$) showed HRE patients ($n = 402$) had less frequent angina (OR = 0.44; 95% CI: 0.30–0.65; $p < 0.001$) and new wall motion abnormalities (OR = 0.63; 95% CI: 0.48–0.83; $p = 0.001$) versus NRE. Karev's 3,434-patient study [22, 23] noted HRE-associated transient global/regional LV dysfunction with blunted ejection fraction augmentation.

Multivariate analysis identified HRE predictors including normal resting force phenotype ($p = 0.003$), LAD stenting history ($p = 0.006$), reduced contractile reserve ($p = 0.005$), resting LAD velocity ($p = 0.004$), and posterior wall thickness ($p = 0.022$). The StressEcho2020 initiative proposed incorporating LV force reserve (peak/rest force ratio) into standard SE protocols, as force measurements remain unaffected by loading conditions, unlike ejection fraction [12]. Our HRE patients showed less frequent contractile reserve impairment (64.3% vs 80.5%, $p = 0.013$), greater resting normal force phenotype prevalence ($p = 0.001$), more exercise supernormal force ($p = 0.048$), and less subnormal force ($p = 0.024$) versus NRE.

The five-step SE protocol analysis revealed no intergroup differences in new wall motion abnormality incidence (step A, $p = 0.601$), consistent with Jurrens TL's findings [31] from 7,015 patients (3,225 without hypertension/CAD). Coronary angiography in 508 patients showed comparable false-positive rates across BP response categories. HRE patients demonstrated significantly higher distal LAD velocities at rest and stress ($p = 0.009$, $p = 0.008$), aligning with hemodynamic principles, though coronary reserve and step D

positivity showed no differences. Contrastingly, Baycan ÖF et al. [29] reported reduced coronary flow reserve in HRE patients (2.06 [1.91–2.36] vs 2.27 [2.08–2.72], $p = 0.004$) due to impaired hyperemic flow (57.5 [51.3–61.5] vs 62.0 [56.0–73.0] cm/s, $p = 0.004$) rather than resting differences (26.5 [22.3–29.8] vs 26.0 [24.0–28.8] cm/s, $p = 0.95$).

Step C positivity (contractile reserve reduction) occurred more frequently in NRE patients ($p = 0.013$), with 2.3-fold greater odds versus HRE, potentially explaining Bouzas-Mosquera C group's findings [33] of worse 10-year outcomes (all-cause mortality, cardiac death, MI, major CV events) in NRE patients ($p < 0.001$).

Given HRE's detrimental effects on LV systolic function, microvascular integrity, and cardiovascular risk amplification, these patients warrant close monitoring and potential antihypertensive regimen optimization. While some reports indicate limited antihypertensive therapy impact on HRE development [33], others note associations with increased ACE-I/ARB [12]. Our study found no significant antihypertensive prescription differences, likely reflecting comparable patient profiles.

Study limitations include a relatively small, heterogeneous population with varying CAD severity, comorbidities, baseline characteristics, and treatment regimens. Large randomized trials remain necessary to clarify relationships between exercise BP response, SE parameters, and their prognostic value in confirmed/suspected CAD patients.

Key findings include:

- Excessive hypertensive responses occur more frequently during horizontal bicycle ergometry and may limit test completion;
- Blood pressure response correlates with SE findings, particularly regarding contractile reserve effects;
- Given contemporary multistage stress testing protocols, further investigation is required to elucidate relationships between BP responses, SE parameters, and their diagnostic/prognostic implications.

Abbreviations

BP: blood pressure

CAD: coronary artery disease

EB: ergometer bicycle

ECG: electrocardiogram

HRE: hypertensive response to exercise

LAD: left anterior descending coronary artery

LVCR: left ventricular contractile reserve

NRE: normotonic response to exercise

RWMA: regional wall motion abnormality

SBP: systolic blood pressure

SE: stress echocardiography

TM: treadmill

VLAD: velocity of the left anterior descending artery

WMSI: wall motion score index

Declarations

Author contributions

TMT: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing. AFS: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing—review & editing. ZDK: Conceptualization, Project administration, Resources, Supervision.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The study "Blood pressure response: impact on the results of ABCDE-stress echocardiography in patients with known and suspected coronary artery disease" was approved by the Ethics Committee of the RUDN Medical Institute (protocol number 29 from 06/20/2024) and the Lazio Ethical Committee 1 as part of the SE-2030 project (protocol No. 295 dated March 8, 2021) and complies with the Declaration of Helsinki (2024 version).

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The data will not be shared because it contains personal data and the privacy of the individual will be violated. For further discussion regarding this study, please contact the corresponding author.

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