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Original Article

Exaggerated exercise blood pressure response and risk of stroke in patients referred for stress testing

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ABSTRACT

Background/objectives: There is some evidence to suggest that exercise systolic blood pressure (SBP) may be associated with future risk of stroke in subjects without a history of coronary artery disease (CAD). However, the value of an exaggerated exercise SBP response (EESBPR) for predicting stroke in patients referred for stress testing for clinical reasons has not been investigated.

Methods: We evaluated a community-based sample of 10,047 patients with known or suspected CAD who underwent treadmill exercise echocardiography. An EESBPR was defined as a peak exercise SBP of >220 mmHg. The ratio of the increase in SBP during exercise to exercise workload (ΔSBPeEW) was also estimated. The endpoints were stroke of any type, ischemic stroke and hemorrhagic stroke. Median follow-up was 3.5 years.

Results: Annualized rates of stroke of any type, ischemic stroke and hemorrhagic stroke were 0.6% (95% CI 0.53–0.67), 0.49% (95% CI 0.42–0.56) and 0.12% (95% CI 0.09–0.15) in patients without EESBPR vs. 0.69% (95% CI 0.37–1), 0.49% (95% CI 0.23–0.76) and 0.19% (95% CI 0.02–0.35) in those with EESBPR ($p = 0.68$, 0.90 and 0.39, respectively). Similarly, there was no significant univariate association between ΔSBPeEW and the occurrence of any endpoint. In multivariate analysis, hypertension, male sex, age, diabetes mellitus and resting SBP remained predictors of stroke of any type. EESBPR and ΔSBPeEW were not predictors of any of the endpoints evaluated.

Conclusion: We did not observe any significant association between exercise SBP and the future occurrence of stroke in patients with known or suspected CAD referred for exercise echocardiography.

1. Introduction

Although resting hypertension is a well-established risk factor for cardiovascular events, the prognostic value of exercise hypertension remains controversial. While some studies reported an association of an exaggerated exercise systolic blood pressure response (EESBPR) with future hypertension [1–7] and cardiovascular events [4,8–10] in healthy subjects, others evaluating patients with known or suspected coronary artery disease (CAD) disagree [11–14]. There is also some evidence to suggest that an EESBPR may be associated with future risk of stroke in middle-aged men without a history of CAD [15]. However, this issue has not been investigated in patients with known or suspected CAD, who represent the majority of subjects referred for noninvasive stress testing in clinical practice.

Our aim was to assess the value of an EESBPR for predicting stroke in patients with known or suspected CAD referred for exercise echocardiography.

2. Methods

2.1. Patients

A total of 13,328 adult patients with known or suspected CAD who underwent treadmill exercise echocardiography at our hospital were initially considered for inclusion. To ensure comprehensive follow-up data, 1113 patients who did not belong to the geographic area of reference of our hospital were excluded. Given that beta-blocker therapy may blunt an EESBPR [16], 1218 patients who received betablockers within 48 h before the tests were also excluded; lastly, because of the well-known association of an exercise hypotensive or flat blood pressure response with poorer outcome [17], 950 patients in whom systolic blood pressure (SBP) failed to increase with exercise above the baseline values were also excluded. The remaining 10,047 patients constituted

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Table 1
Baseline characteristics of the patients.

	All patients (n = 10047)	No EESBPR (n = 9645)	EESBPR (n = 402)	p
Male, n (%)	6105 (60.8)	5861 (60.8)	244 (60.7)	0.97
Age, years	62.0 ± 12.2	62.0 ± 12.1	61.7 ± 10.3	0.51
Current smokers, n (%)	2504 (24.9)	2408 (25)	96 (23.9)	0.62
Diabetes, n (%)	1810 (18)	1722 (17.9)	88 (21.9)	0.04
Hypertension, n (%)	5227 (52)	4935 (51.2)	291 (72.4)	<0.001
Hypercholesterolemia, n (%)	4759 (47.4)	4560 (47.3)	199 (49.5)	0.38
Family history of CAD, n (%)	1305 (13)	1237 (12.8)	68 (16.9)	0.02
History of CAD, n (%)	2519 (25.1)	2447 (25.4)	72 (17.9)	0.001
Prior myocardial infarction, n (%)	1900 (18.9)	1846 (19.1)	54 (13.4)	0.004
≤30 days before EE, n (%)	850 (8.5)	829 (8.6)	21 (5.2)	0.02
>30 days before EE, n (%)	1096 (10.9)	1063 (11)	33 (8.2)	0.08
Prior coronary revascularization, n (%)	1534 (15.3)	1486 (15.4)	48 (11.9)	0.06
PCI, n (%)	1046 (10.4)	1014 (10.5)	32 (8)	0.10
CABG, n (%)	795 (7.9)	770 (8)	25 (6.2)	0.20
Chest pain, n (%)				
Typical angina, n (%)	778 (7.7)	758 (7.9)	20 (5)	0.03
Atypical/probable angina, n (%)	4251 (42.3)	4049 (42)	202 (50.2)	0.001
Nonanginal chest pain, n (%)	2302 (22.9)	2229 (23.1)	73 (18.2)	0.02
Dyspnea, n (%)	599 (6)	583 (6)	16 (4)	0.09
Uninterpretable resting ECG, n (%)	2354 (23.4)	2256 (23.4)	98 (24.4)	0.65
Left bundle branch block, n (%)	669 (6.7)	643 (6.7)	26 (6.5)	0.88
Atrial fibrillation, n (%)	453 (4.5)	448 (4.6)	5 (1.2)	0.001
ACE-i/ARB, n (%)	3381 (33.7)	3235 (33.5)	146 (36.3)	0.24
Nitrates, n (%)	2207 (22)	2133 (22.1)	75 (18.7)	0.11
Calcium channel blockers, n (%)	900 (9)	861 (8.9)	39 (9.7)	0.59

ACE-i denotes angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; CAD, coronary artery disease; ECG, electrocardiogram; EE, exercise echocardiography; EESBPR, exaggerated exercise systolic blood pressure response; PCI, percutaneous coronary intervention.

our sample. This study was approved by the Clinical Investigation Ethics Committee of Galicia.

2.2. Data collection

Demographics, clinical data and stress testing results were entered in a dedicated database at the time of testing. Hypertension, hypercholesterolemia, and diabetes mellitus were defined on the basis of history and antihypertensive, lipid-lowering, or antidiabetic treatment, respectively. Patients referred for evaluation of chest pain were classified as having typical angina, atypical/probable angina or nonischemic chest pain [18]. A history of CAD was defined as previous myocardial infarction, previous coronary revascularization or prior angiographic documentation of any ≥50% coronary stenosis. Resting ECG was considered uninterpretable in the presence of left bundle branch block, paced rhythm, left ventricular hypertrophy with strain, treatment with digoxin, preexcitation, or other repolarization abnormalities.

All patients underwent symptom-limited treadmill exercise echocardiography. Protocols employed included the Bruce protocol in 8676 patients (86.4%), the modified Bruce protocol in 464 patients (4.6%), the Naughton protocol in 104 patients (1%), and other protocols in 803 patients (8%). Heart rate, blood pressure, and a 12-lead electrocardiogram were recorded at rest and at each stage of the protocol. Peak SBP was defined as the maximum value of SBP obtained during exercise.

Table 2
Data provided by exercise stress testing.

	All patients (n = 10047)	No EESBPR (n = 9645)	EESBPR (n = 402)	p
Systolic blood pressure, mm Hg				
Rest	133 ± 19	132 ± 18	161 ± 23	<0.001
Peak	171 ± 30	168 ± 25	243 ± 56	<0.001
Heart rate, beats/min				
Rest	79 ± 15	79 ± 14.8	80 ± 14	0.19
Peak	149 ± 20	149 ± 21	148 ± 18	0.22
RPP, $\times 10^3$ mm Hg beats/min				
Rest	10.5 ± 2.6	10.4 ± 2.5	12.9 ± 3.1	<0.001
Peak	25.6 ± 5.8	25.1 ± 5.3	34.7 ± 7.7	<0.001
% of MAPHR	94.1 ± 11.5	94.1 ± 11.5	93.1 ± 10.3	0.08
Submaximal test, n (%)	1831 (18.2)	1747 (18.1)	84 (20.9)	0.15
Exercise-induced chest pain, n (%)	1368 (13.6)	1335 (13.8)	33 (8.2)	0.001
Ischemic ECG changes, n (%)	1478 (14.7)	1413 (14.7)	65 (16.2)	0.4
Exercise workload, METs	9.5 ± 3.1	9.5 ± 3.2	8.3 ± 2.5	<0.001
Left ventricular ejection fraction, %				
Rest	58.4 ± 8.2	58.3 ± 8.2	60.3 ± 6.7	<0.001
Peak	63.2 ± 12.3	63.1 ± 12.3	65.1 ± 10.5	0.002
Resting wall motion abnormalities, n (%)	2055 (20.5)	1998 (20.7)	57 (14.2)	0.001
Echocardiographic ischemia, n (%)	2744 (27.3)	2653 (27.5)	91 (22.6)	0.03
Wall motion score index				
Rest	1.09 ± 0.24	1.09 ± 0.23	1.05 ± 0.18	0.001
Peak	1.18 ± 0.32	1.19 ± 0.24	1.14 ± 0.27	0.007

ECG denotes electrocardiographic; EESBPR, exaggerated exercise systolic blood pressure response; MAPHR, maximum age-predicted heart rate; METs, metabolic equivalents; RPP, rate-pressure product.