Original articles

An exaggerated systolic blood pressure response to exercise is associated with cardiovascular remodeling in subjects with prehypertension

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Blood pressure; Exercise; Hypertension; Target organ damage.

Background. **Although many observers consider the cardiovascular risk associated with isolated prehypertension to be low and not worth pharmacological treating, the cardiovascular disease rate is increased among individuals within this blood pressure stratum.**

Methods. **We performed Doppler echocardiography and submaximal bicycle ergometry in 20 nonsmoking sedentary prehypertensive subjects and 20 age- and sex-matched nonsmoking sedentary normotensive subjects, and investigated the association between the systolic blood pressure response to exercise (SBPRE) and hypertensive target organ damage. An exaggerated SBPRE (E-SBPRE) and a normal SBPRE (N-SBPRE) were diagnosed using the mean +2 standard deviations of systolic blood pressure at 100 W in normotensives.**

Results. **Body mass index was similar in the two groups. Resting blood pressure and systemic vascular resistance were higher in prehypertensives. Almost half the latter had an E-SBPRE. There were no differences in age, gender, and body mass index between normotensives and prehypertensives with an E-SBPRE or a N-SBPRE. Resting blood pressure and systemic vascular resistance were similarly increased in prehypertensives with an E-SBPRE and a N-SBPRE vs normotensives. Compared with normotensives, prehypertensives with an E-SBPRE showed: a) a significantly greater left ventricular relative wall thickness, mostly due to a smaller cavity, b) a significantly longer left ventricular isovolumic relaxation time, and c) a significantly greater global arterial stiffness, as estimated by the pulse pressure/left ventricular stroke volume ratio.**

Conclusions. **Our findings suggest that an E-SBPRE is frequent among prehypertensive subjects and is associated with cardiovascular remodeling, which may herald cardiovascular disease.**

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Introduction

Many observers consider that a blood pressure of 120-139/80-89 mmHg is indicative of subjects with prehypertension and suggest that, without compelling indications for pharmacological treatment, these people should undergo frequent blood pressure testing and be advised to reduce lifestyle risk factors for cardiovascular disease[1]. However, longitudinal investigations show that the cardiovascular disease rate is increased among individuals within this blood pressure stratum compared with normotensive individuals (blood pressure < 120/80 mmHg)[2,3], fuelling concern about the accuracy of the present categorization approach of blood pressure in estimating the cardiovascular risk associated with isolated prehypertension.

Pathophysiologically elevated blood pressure in response to daily recurring stress cannot be unequivocally identified by sporadic measurements of resting blood pressure[4]. By contrast, there is convincing evidence that systolic blood pressure response to exercise (SBPRE) is an indicator of hypertensive target organ damage and other cardiovascular complications[5-8].

We have investigated whether the SBPRE may help identify, among prehypertensive subjects, those with hypertensive target organ damage, which may herald cardiovascular disease.

Methods

Twenty nonsmoking sedentary prehypertensives and 20 age- and sex-matched nonsmoking sedentary normotensive indi-

viduals at repeated checks were recruited from a large pool of outpatients evaluated for chest pain syndromes or palpitation. Entry criteria were: no documented history of ischemic heart disease, systemic hypertension (blood pressure ≥ 140/90 mmHg), diabetes mellitus, dyslipidemia, renal disease or endocrine disorders; no assumption of medications; and the presence of sinus rhythm and normal QRS complex and ST/T on standard 12-lead ECG. All participants gave written consent to the study after being informed about the aim and procedures. On the day of investigation, participants reported to the laboratory in the morning while in fasting condition. Height and weight were measured, and venous blood was sampled for lipid profile assessment by standard assay. Then they underwent Doppler echocardiography and, subsequently, bicycle ergometry, which were performed before noon on the same day.

Doppler echocardiography. A single experienced investigator, blinded to the subject's clinical data and exercise testing, performed and read all echocardiographic studies. A detailed two-dimensional, Doppler echocardiogram (Apogee CX, ATL, Ambler, PA, USA) was obtained for all participants while they were in a supine lateral position after resting for 30 min, according to the American Society of Echocardiography recommendations[9]. Three cardiac cycles were averaged for measurements. Mean blood pressure and pulse pressure were calculated from systolic and diastolic blood pressure measured 3 times in the left arm by indirect cuff-sphygmomanometry after the echocardiographic study with subjects in supine decubitus. Heart rate was calculated as 60/the time between two consecutive QRS complexes from simultaneous ECG on echo-tracings. Left ventricular M-mode measurements of wall thickness and end-diastolic and end-systolic diameters were obtained according to the Penn convention[10], and used to calculate relative wall thickness and left ventricular mass[11], and to estimate left ventricular end-diastolic and end-systolic volumes with the Teichholz formula[12]. The latter estimates were used to derive left ventricular stroke volume and ejection fraction, and to compute cardiac output and systemic vascular resistance according to standard formulae. Left ventricular function was assessed in the apical 4-chamber view. Early and late transmitral peak flow velocities from pulsed-wave Doppler imaging were measured at the tip of the valve. Isovolumic relaxation time, i.e. the time from the end of transaortic flow to the onset of early diastolic flow, was measured by placing the continuous-wave cursor Doppler beam across the left ventricular outflow tract near the mitral valve anterior leaflet[13]. The ratio of pulse pressure-to-stroke volume was used to estimate total arterial stiffness[14].

Bicycle ergometry and definition of systolic blood pressure response to exercise. A single experienced investigator, blinded to the subject's clinical data and echocardiography, supervised all exercise tests. Ergometry was performed on a mechanically braked bicycle. The protocol began at a workload of 25 W and increased by 25 W every 2 min up to 100 W. Throughout exercise, ECG was monitored and blood pressure was obtained in the left arm by indirect cuff-sphygmomanometry during the last minute of each stage. Prehypertensive subjects were diagnosed as having an exaggerated SBPRE (E-SBPRE) and a normal SBPRE (N-SBPRE) using the mean +2 standard deviations (SD) of systolic blood pressure at 100 W in normotensive subjects.

Statistical analysis. Numeric variables are expressed as mean value ± SD. We used the two-tailed unpaired Student's t-test and the χ^2 test to identify differences between normotensives and prehypertensives. For comparisons between normotensives and prehypertensives with a N-SBPRE or an E-SBPRE we used the χ^2 test and ANOVA with *post-hoc* multiple comparisons assessed with the Bonferroni method, adjusting for three-way comparisons. Bivariate Pearson's correlation was used to evaluate relationships between continuous variables. Data were analyzed with standard statistical software (SPSS version 9, SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered as statistically significant.

Results

Normotensive and prehypertensive individuals had a similar body size, lipid profile, and resting heart rate (Table I). Resting systolic, diastolic and mean blood pressure were higher in prehypertensives than in normotensives, whereas pulse pressure was comparable. Doppler echocardiography showed that all participants had normal regional and global resting left ventricular function and none had significant (> mild) valvular dysfunction or left ventricular hypertrophy defined as a left ventricular mass index > 116 g/m^2 in men and > 104 g/m^2 in women[15]. There were no differences between the two groups as to left ventricular size and geometry, left ventricular chamber systolic and diastolic function, cardiac index, and total arterial stiffness, but prehypertensives had higher systemic vascular resistance vs normotensives.

All participants had negative exercise ECG for inducible myocardial ischemia and arrhythmias up to 100 W. In normotensives, systolic blood pressure progressively increased in response to staged exercise, and reached 178 ± 7 mmHg at 100 W (Fig. 1). Thus, with the mean +2 SD of systolic blood pressure at 100 W in normotensives (192 mmHg) as the normal maximum value of systolic blood pressure at 100 W, the ergometric procedure revealed that 48% of prehypertensives had an E-SBPRE. However, while systolic blood pressure gradually increased in prehypertensives with a

Table I. Clinical characteristics and cardiovascular variables of normotensives (NT) and prehypertensives (PH).

	NT (n=20)	PH (n=20)
Age (years)	40 ± 6	39 ± 8
Sex (M/F)	14/6	14/6
Body mass index (kg/m^2)	25 ± 1	25 ± 1
Total cholesterol (mg/dl)	182 ± 8	180 ± 10
HDL cholesterol (mg/dl)	45 ± 6	44 ± 7
Triglycerides (mg/dl)	169 ± 12	167 ± 14
Heart rate (b/min)	70 ± 6	72 ± 7
Systolic blood pressure (mmHg)	115 ± 3	131 ± 3*
Diastolic blood pressure (mmHg)	69 ± 4	84 ± 2*
Mean blood pressure (mmHg)	84 ± 3	99 ± 2*
Pulse pressure (mmHg)	46 ± 4	47 ± 3
End-diastolic diameter (mm)	49 ± 3	48 ± 3
Interventricular septum (mm)	9.0 ± 0.6	9.1 ± 0.5
Posterior wall thickness (mm)	9.0 ± 0.5	9.1 ± 0.6
Left ventricular mass index (g/m^2)	94 ± 15	92 ± 14
Relative wall thickness	0.37 ± 0.03	0.38 ± 0.03
Ejection fraction (%)	66 ± 7	68 ± 6
Stroke index (ml/m^2)	39 ± 5	39 ± 6
E/A ratio	1.27 ± 0.19	1.23 ± 0.14
Isovolumic relaxation time (ms)	80 ± 11	86 ± 12
Cardiac index (l/min/m^2)	2.8 ± 0.3	2.8 ± 0.4
Systemic vascular resistance (dyne·s/cm^5)	1315 ± 181	1579 ± 220*
Pulse pressure/stroke volume (mmHg/ml)	0.63 ± 0.11	0.67 ± 0.10

E/A = early-to-late ratio of transmitral peak flow velocities; HDL = high-density lipoprotein. * $p < 0.001$ vs NT.

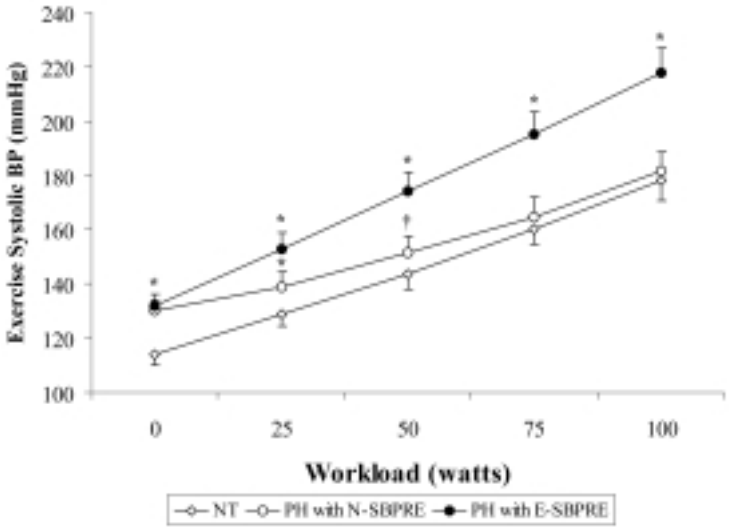

Figure 1. *Exercise systolic blood pressure (BP) in normotensives (NT) and in prehypertensives (PH) with normal (N-SBPRE) or exaggerated (E-SBPRE) systolic blood pressure response to exercise. * $p < 0.001$ and † $p < 0.005$ vs the corresponding values in NT.*

N-SBPRE and, above 50 W, practically coincided with that of normotensives, systolic blood pressure was higher in prehypertensives with an E-SBPRE than in normotensives at each stage of exercise, and reached 218 ± 9 mmHg at 100 W (Fig. 1). In the whole prehypertensive group, systolic blood pressure at 100 W did not correlate with resting blood pressure indexes (all $p > 0.1$). Normotensives and the two prehypertensive subgroups (with a N-SBPRE or an E-SPBRE) did not differ as to exercise heart rate (118 ± 6, 121 ± 8 and 124 ± 9 b/min, ANOVA $p > 0.05$) and diastolic blood pressure (68 ± 8, 75 ± 12 and 71 ± 10 mmHg, ANOVA $p > 0.1$) at 100 W.

Normotensives and the two prehypertensive subgroups had a similar age, gender, body size, and resting heart rate (Table II). The resting systolic, diastolic and mean blood pressure of the prehypertensive subgroups were comparably higher than those of normotensives, whereas pulse pressure was similar in the three groups. Compared with normotensives, prehypertensives with

Table II. Clinical characteristics and cardiovascular variables of normotensives (NT) and prehypertensives (PH) with exaggerated (E-SBPRE) and normal (N-SBPRE) systolic blood pressure response to exercise.

	NT (n=20)	PH		p ANOVA
		N-SBPRE (n=11)	E-SBPRE (n=9)	
Age (years)	40 ± 6	38 ± 7	41 ± 9	NS
Sex (M/F)	14/6	8/3	6/3	NS
Body mass index (kg/m^2)	25 ± 1	24 ± 1	25 ± 1	NS
Total cholesterol (mg/dl)	182 ± 8	181 ± 11	178 ± 11	NS
HDL cholesterol (mg/dl)	45 ± 6	43 ± 6	44 ± 7	NS
Triglycerides (mg/dl)	169 ± 12	163 ± 14	172 ± 13	NS
Heart rate (b/min)	70 ± 6	71 ± 8	73 ± 7	NS
Systolic blood pressure (mmHg)	115 ± 3	130 ± 3*	132 ± 1*	< 0.001
Diastolic blood pressure (mmHg)	69 ± 4	84 ± 2*	83 ± 2*	< 0.001
Mean blood pressure (mmHg)	84 ± 3	99 ± 2*	99 ± 2*	< 0.001
Pulse pressure (mmHg)	46 ± 4	46 ± 3	49 ± 2	NS
End-diastolic diameter (mm)	49 ± 3	49 ± 2	46 ± 3$^{\S\#}$	< 0.05
Interventricular septum (mm)	9.0 ± 0.6	8.9 ± 0.5	9.4 ± 0.5	NS
Posterior wall thickness (mm)	9.0 ± 0.5	8.9 ± 0.7	9.3 ± 0.4	NS
Left ventricular mass index (g/m^2)	94 ± 15	94 ± 15	89 ± 13	NS
Relative wall thickness	0.37 ± 0.03	0.36 ± 0.02	0.40 ± 0.01$^{\dagger\circ}$	< 0.001
Ejection fraction (%)	66 ± 7	67 ± 6	69 ± 5	NS
Stroke index (ml/m^2)	39 ± 5	41 ± 6	36 ± 5	NS
E/A ratio	1.27 ± 0.19	1.27 ± 0.12	1.19 ± 0.16	NS
Isovolumic relaxation time (ms)	80 ± 11	80 ± 9	94 ± 12$^{\ddagger\#}$	< 0.01
Cardiac index (l/min/m^2)	2.8 ± 0.3	2.9 ± 0.4	2.6 ± 0.4	NS
Systemic vascular resistance (dyne·s/cm^5)	1315 ± 181	1522 ± 196§	1649 ± 239°	< 0.001
Pulse pressure/stroke volume (mmHg/ml)	0.63 ± 0.11	0.61 ± 0.08	0.73 ± 0.08$^{\S\#}$	< 0.05

E/A = early-to-late ratio of transmitral peak flow velocities; HDL = high-density lipoprotein. * $p < 0.001$, † $p < 0.005$, ‡ $p < 0.01$, § $p < 0.05$ vs NT; $^{\circ}$ $p < 0.005$, $^{\#}$ $p < 0.05$ vs PH with N-SBPRE.

a N-SBPRE had similar left ventricular characteristics, cardiac index and total arterial stiffness, but higher systemic vascular resistance. Conversely, prehypertensives with an E-SBPRE had a smaller left ventricular end-diastolic diameter and marginally thicker left ventricular walls vs normotensives, thereby resulting in higher relative wall thickness and a comparable left ventricular mass index. Neither left ventricular chamber systolic function nor the early-to-late ratio of transmitral peak flow velocities of prehypertensives with an E-SBPRE differed vs normotensives, whereas the isovolumic relaxation time was longer in prehypertensives with an E-SBPRE than in normotensives. The cardiac index was similar in the two groups, but prehypertensives with an E-SBPRE had higher systemic vascular resistance and total arterial stiffness vs normotensives.

Discussion

The novel finding of our cross-sectional study is that an E-SBPRE is frequent among prehypertensive subjects and is associated with cardiovascular remodeling, which may herald cardiovascular disease[2,3]. Thus, pathophysiologically elevated systolic blood pressure in response to daily recurring physical stress may have a key role in the development of hypertensive cardiovascular damage and hence its recognition may provide a better stratification of the cardiovascular risk associated with prehypertension.

Our prehypertensive subjects had higher systemic vascular resistance and a similar cardiac index compared with normotensive individuals, which suggests that vascular impairment is already present in prehypertension. Apart from the difference in hemodynamic profile, the two groups had comparable left ventricular and arterial characteristics, indicating that prehypertension *per se* is not associated with detectable cardiovascular remodeling. Our data contrast with reports of altered cardiac morphological features[16] and diastolic left ventricular dysfunction[17] in individuals with high-normal blood pressure (130-139/85-89 mmHg) compared to subjects with normal (120-129/80-84 mmHg) or optimal resting blood pressure (< 120/80 mmHg). This discrepancy is not surprising because the blood pressure range used to diagnose prehypertension (120-139/80-89 mmHg) encompasses values previously considered as "normal".

Systolic blood pressure at rest is reported to be an independent predictor of exercise systolic blood pressure, which explains over 40% of the interindividual variability[18]. However, in line with other observations[19,20], we did not find any correlation between resting blood pressure indexes and systolic blood pressure at 100 W in prehypertensives. Thus, our study reinforces the concept that the measurement of resting

blood pressure on single occasions may not identify periodic surges in blood pressure related to exertion and emotional stress[4]. Differently, exercise testing identifies pathophysiologically elevated blood pressure in response to daily recurring physical stress, which would pass unnoticed on the basis of resting blood pressure testing. From a diagnostic viewpoint, this information is of major relevance since it would help distinguish "true prehypertensive" subjects from "false prehypertensive" subjects, i.e. individuals probably affected by "white coat" prehypertension.

It is difficult to explain the association of an E-SBPRE with cardiovascular remodeling. Arterial stiffness makes a major contribution to exercise systolic blood pressure[21], to concentric left ventricular remodeling[22] and to delayed left ventricular relaxation[23]. Therefore, enhanced arterial wall stiffness may have provided the substrate for the association of an E-SBPRE with abnormalities in left ventricular structure and diastolic function observed in our study. Of note, normotensives and the two prehypertensive subgroups (with N-SBPRE or E-SBPRE) had similar resting and submaximal exercise heart rate. Therefore, it seems unlikely that sympathetic overactivity, which is emerging as an independent risk factor for the development of hypertension and its complications[24], may have accounted for the cardiovascular alterations detected in our prehypertensive subjects with E-SBPRE. However, since we did not specifically investigate the status of the sympatho-vagal balance (e.g., through spectral analysis of heart rate variability), we cannot exclude that a subtle sympathetic predominance among our prehypertensives might have contributed to the association between cardiovascular remodeling and E-SBPRE. Furthermore, consistent with a previous report[25], we found no association between an E-SBPRE and increased left ventricular mass in our prehypertensive subjects. Previous studies suggest that the major determinants of left ventricular mass in hypertension are increased preload and/or reduced myocardial inotropic state associated with elevated systemic vascular resistance, rather than the blood pressure regimen *per se*[26]. Indeed, although systemic vascular resistance was remarkably increased in our prehypertensives with an E-SBPRE, it was associated with a reduced stroke and cardiac index and preserved left ventricular chamber systolic function, which points to a reduced preload with a normal or even enhanced myocardial inotropic state. Interestingly, studies in never-treated and uncomplicated mild-to-moderate hypertension found that, in some patients, concentric left ventricular remodeling and diastolic dysfunction due to impaired myocardial relaxation may represent an early stage of cardiac involvement, which is usually associated with increased total arterial stiffness, elevated systemic arterial stiffness, and decreased cardiac index due to reduced left ventricular cavity and blood volume[27-29]. Based on these considerations, and the finding that prehypertensives have an increased risk of progressing to hypertension[30], and that a hypertensive exercise response is an additional risk factor for new-onset hypertension[31], the early recognition of E-SBPRE in prehypertension may reveal subjects who are prone to develop hypertension associated with a specific hypertensive cardiovascular phenotype (i.e., concentric left ventricular remodeling and increased arterial wall stiffness), which confers a high risk of cardiovascular events[32-34].

Our results diverge from the observation by Mottram et al.[35] that, compared with normotensives without a hypertensive response to exercise, subjects with a high-normal resting blood pressure and a hypertensive response to exercise had impaired left ventricular long-axis systolic function without global diastolic dysfunction or abnormalities of left ventricular morphology. However, their subjects were about 10 years older than our prehypertensive subjects, and hence had been affected by prehypertension for a longer time, potentially indicative of a different stage of the hypertensive disease. In addition, unlike our study, over half the subjects reported by Mottram et al.[35] were women and hypercholesterolemic, some were smokers and others were frankly obese. Therefore, interaction between these factors might have influenced the cardiovascular phenotype. Moreover, the hypertensive response to exercise was defined on the basis of exercise blood pressure at maximal exertion, which was previously used to assess the risk for established hypertension[36,37]. By contrast, in our study exercise blood pressure reactivity was defined using the mean +2 SD of systolic blood pressure in normotensive subjects at submaximal effort, i.e. at workloads more reasonably reflective of normal daily activities. We therefore suspect that defining hypertensive response to exercise using blood pressure at maximal and submaximal effort might have different pathophysiological and prognostic implications during systemic hypertension. Indeed, in a recent study of patients with untreated mild hypertension (high-normal resting blood pressure or stage 1-2 hypertension), Pierson et al.[38] found that a greater left ventricular relative wall thickness was associated with a higher submaximal systolic blood pressure, whereas it was not related to peak exercise systolic blood pressure.

Although the reproducibility of blood pressure response during bicycle ergometry has not been studied in our study, earlier reports[39-41] have indicated a good reproducibility for blood pressure measured during exercise. In addition, it has been shown that measurement of blood pressure at low-to-moderate workloads, as done in our study, not only requires a minimum of subject cooperation and diminishes the potential effect of interindividual differences in habitual physical activity, but is also easier to measure and more accurate, thereby yielding more objective and reproducible results[42]. However, in 117 healthy subjects with an exaggerated blood pressure response to exercise (diagnosed as a peak systolic blood pressure and/or diastolic blood

pressure > 200 and > 100 mmHg, respectively), who performed 2 to 7 consecutive treadmill exercise tests over 25 years, Sharabi et al.[43] reported that only about one sixth of them had at least two third repetitions of the exaggerated blood pressure response to exercise over time. Indeed, whether similar results would have been obtained by using submaximal instead of maximal blood pressure measurements is uncertain. Moreover, it is unclear as to whether an exaggerated blood pressure response to exercise marks a stage of the hypertensive disease or whether it is a consistent feature over time.

In conclusion, the high prevalence of E-SPBRE among individuals with prehypertension and its association with cardiovascular remodeling found in our study suggests that pathophysiologically elevated systolic blood pressure in response to daily recurring physical stress may play an important role in the development of hypertensive cardiovascular damage and that its early recognition in prehypertension may help to identify subjects with a more elevated cardiovascular risk who would perhaps benefit from more aggressive treatment. Indeed, previous studies have demonstrated that a careful investigation of tissue organ damage in hypertension may dramatically influence the crude cardiovascular risk stratification based on resting blood pressure, and hence identify patients who would benefit from drug therapy[44].

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