

Anticipatory Blood Pressure Response to Exercise Predicts Future High Blood Pressure in Middle-aged Men

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Abstract Increases in blood pressure during the period of emotional arousal attendant to impending exertion are well documented, yet the etiologic significance of these elevations is unknown. Research suggests that exaggerated cardiovascular responses to psychological stress may be importantly related to hypertension. We examined blood pressure reactivity in anticipation of an exercise stress test in relation to future hypertension in the Kuopio Ischemic Heart Disease Risk Factor Study, a population-based study of middle-aged men from Eastern Finland. Subjects were 508 unmedicated men with resting blood pressure less than 165/95 mm Hg who completed a bicycle ergometer stress test at baseline and whose hypertensive status was assessed at 4 years of follow-up. Systolic and diastolic reactivity were calculated as the difference between blood pressure measured after seated rest on the bicycle ergometer before initiation of exercise and mean seated resting blood pressure measured 1 week earlier. Logistic regression

models adjusted for age and resting blood pressure revealed a graded association between quartiles of reactivity and risk of subsequent hypertension ($\geq 165/95$ mm Hg), with men showing systolic responses greater than or equal to 30 mm Hg or diastolic responses greater than 15 mm Hg at nearly four times the risk of becoming hypertensive (odds ratios, 3.80 [95% confidence interval, 1.90 to 7.63] and 3.65 [95% confidence interval, 1.86 to 7.17], respectively) relative to the least-reactive groups (systolic response, < 10 mm Hg; diastolic response, < 5 mm Hg). Adjustments for traditional risk factors for hypertension did not alter these associations. Results demonstrate the clinical significance of the pressor response in anticipation of exercise and support the hypothesis that cardiovascular reactivity to psychological challenge plays a role in the etiology of hypertension. (*Hypertension*. 1996;27:1059-1064.)

Key Words • cardiovascular system • hypertension • exercise • blood pressure • risk factors

Exaggerated BP responses during both dynamic and isometric exercise are associated with increased risk of future hypertension.¹⁻⁴ Surprisingly, BP increases in anticipation of exercise, which are well documented,⁵ have not been examined in relation to hypertension risk. The period preceding exercise can be characterized as a period of emotional, behavioral, and physiological arousal attendant to an impending challenge. Thus, BP elevations in anticipation of exercise reflect cardiovascular adjustments in response to psychological and behavioral stresses, a phenomenon described as cardiovascular reactivity.⁶

Several lines of evidence suggest that behaviorally induced cardiovascular reactivity may be causally related to and/or a risk marker for hypertension.^{7,8} Research with spontaneously hypertensive rats has found that the prehypertensive state is accompanied by exaggerated nervous system reactivity that contributes to the progression of the hypertension,^{9,10} a process that is accelerated by exposure to long-term stress.¹¹ Among humans, men at greatest risk

for hypertension, determined by high normal resting BP and/or a parental history of hypertension, also show the most exaggerated BP responses during casual stethoscopic readings (a "white coat" effect)^{12,13} and during standard laboratory challenges.¹⁴⁻¹⁷ Also, borderline hypertensive individuals (SBP=140 to 164 mm Hg and/or DBP=90 to 94 mm Hg) show exaggerated heart rate and/or BP responses to various stressors relative to normotensive individuals.¹⁸⁻²¹

Nonetheless, support for the reactivity hypothesis is limited at present, largely because of a lack of adequate and appropriate prospective studies^{8,22} and/or the use of selected or convenience samples (eg, male medical students or military officers²³⁻²⁶). Some early studies, which relied solely on the cold pressor test, found that "hyperreactors" to the cold pressor test were more likely to develop hypertension over time.^{25,27-29} Others, however, have failed to identify such an association.^{23,24,26} It also has been shown that exaggerated BP responses to tasks requiring a more active behavioral component than that required by the cold pressor test (eg, serial subtraction task, unsignaled reaction time task, isometric handgrip) are associated with higher, albeit still normotensive, BP levels 6 to 15 years later.^{13,30} Thus, it remains to be seen whether exaggerated BP responses to a psychologically challenging stressor predict future hypertension.

The present study examined the relationship between cardiovascular reactivity to a psychological stressor, ie, BP elevations in anticipation of a bicycle ergometer stress test, and subsequent high BP in a randomly selected, population-based sample of middle-aged men. This report is from the Kuopio Ischemic Heart Disease

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Selected Abbreviations and Acronyms

| |
|--------------------------------|
| BP = blood pressure |
| CI = confidence interval |
| DBP = diastolic blood pressure |
| OR = odds ratio |
| SBP = systolic blood pressure |

Risk Factor Study (KIHD), designed in part to examine associations between promising but unestablished behavioral and psychosocial risk factors and cardiovascular diseases and other outcomes.³¹ Available data on health habits, family illness history, and various anthropometric and demographic measures enabled us to examine potential confounding influences of other risk factors for hypertension.

Methods

Study Population

The KIHD study is an ongoing, population-based study designed to investigate previously unestablished risk factors for carotid atherosclerosis, ischemic heart disease, mortality, and other outcomes among middle-aged men from the Kuopio region in Eastern Finland, an area of high coronary morbidity and mortality.³² A total of 2682 participants (82.9% of those eligible), aged 42, 48, 54, or 60 years, were enrolled in the study between March 1984 and December 1989. Follow-up examinations were conducted between March 1991 and December 1993 on those men who had undergone ultrasound-examination of the right and left carotid arteries at baseline. A total of 1229 were eligible for the follow-up study; of these, 52 had died, were unable to participate because they were suffering severe illness or had migrated away from the region, and 139 could not be contacted or refused to participate. Thus, the follow-up study included 1038 participants or 88.2% of those eligible and able to participate. Average time to follow-up was 4.1 years (range, 2.3 to 5.2 years).

For the present analyses, subjects were excluded if they had missing BP data at baseline or follow-up ($n=10$), were hypertensive (according to World Health Organization criteria, ie, BP $\geq 165/95$ mm Hg or on antihypertensive medications) ($n=345$), did not participate in the bicycle ergometer test ($n=97$), or had missing data on the covariates at baseline ($n=78$). Thus, the results reported herein are based on 508 initially normotensive men who performed the exercise tolerance test at baseline and had complete information on covariates at baseline and hypertension status at follow-up. Subject characteristics are shown in Table 1. A comparison of the 175 KIHD participants with missing data on the bicycle ergometer test and/or baseline covariates with the 508 subjects with

complete data revealed no significant differences in baseline resting BP or body mass index (both $P>.18$).

Baseline and Follow-up Examinations

Examinations were carried out over 2 days, 1 week apart, at both baseline and follow-up and consisted of a wide variety of biochemical, physiological, anthropometric, and psychosocial measures. In addition, a linear-slope maximal exercise tolerance test on an upright bicycle ergometer was administered at the baseline exam. Medical history and medication use were checked during a medical examination at both baseline and follow-up.

BP Measurement and Reactivity Assessment

The BP data used in the present analyses were obtained on two occasions by a trained observer using a random-zero muddler sphygmomanometer (Hawksley). The BP measurement protocol on the first examination day was as follows: 15 minutes of supine rest with BP measured at minutes 5, 10, and 15; standing rest with one BP reading taken after 1 minute; and 10 minutes of seated rest with BP measured at minutes 5 and 10. For the present analyses, the averages of the two seated SBP and DBP measurements were considered resting SBP and DBP, respectively. A second measure of sitting BP was obtained on the second examination day 1 week later after the subject had been seated on the bicycle ergometer for 5 minutes but before the exercise test protocol was begun. Measurements on both examination days occurred in the mornings. Anticipatory SBP and DBP responses (SBP Δ , DBP Δ) were calculated as the difference between the seated BP reading obtained before exercise and the mean seated resting BP obtained on the first examination day.

These SBP and DBP responses in anticipation of exercise constituted our measures of cardiovascular reactivity. Prior studies of reactivity have not used a preexercise period as a stressor; however, participants were encouraged to perform at their best level and knew that the results of the test would be an indicator of their cardiovascular health status. In an area with known high rates of cardiovascular morbidity and mortality,³² this impending knowledge could be particularly stress inducing. Furthermore, any increase in BP that occurred during this anticipatory period was in excess of metabolic demand because physical work had not yet begun and thus could be attributed to the person's psychological response to the demand characteristics of the setting. Research has shown that this anticipatory response is characterized by an interplay of neural, hormonal, and mechanical factors that ready the cardiovascular system for the impending exertion, is cerebral in origin, and is most likely to occur in situations with a high degree of emotional involvement.⁵

Hypertensive Status at Follow-up

The BP measurement protocol at follow-up was identical to that of the baseline protocol, with resting SBP and DBP calculated as the averages of two seated measurements obtained at minutes 5 and 10 of a 10-minute seated rest. A subject was considered to be hypertensive at the 4-year follow-up exam if his resting SBP was greater than or equal to 165 mm Hg or his resting DBP was greater than or equal to 95 mm Hg or if he was currently taking antihypertensive medications. A total of 116 men (22.8%) met these criteria.

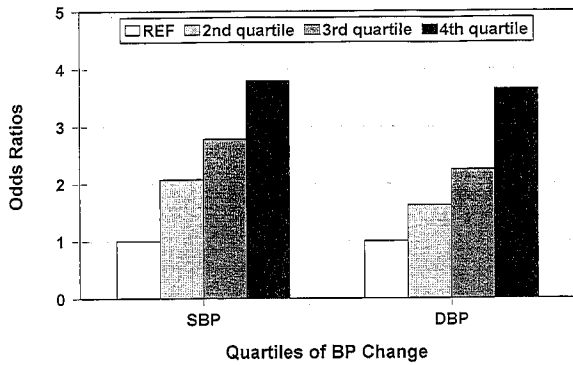
Data Analyses

The relation between SBP Δ and hypertensive status was assessed with a series of age-adjusted logistic regression models with the anticipatory responses modeled both continuously and categorically. (Categories of anticipatory BP responses were created on the basis of natural breaks in the distribution of scores for SBP Δ and DBP Δ . These categories formed approximate quartiles as follows. SBP Δ : <10 mm Hg, 25.6%; 10 to 19 mm Hg, 24.2%; 20 to 29 mm Hg, 26.2%; ≥ 30 mm Hg, 24.0%. DBP Δ : <5 mm Hg, 25.9%; 5 to 9 mm Hg, 27.9%; 10 to 15

TABLE 1. Subject Characteristics

| Characteristic | Value |
|------------------------------------|--------------|
| n | 508 |
| Age, y | 51.0 (6.7) |
| Body mass index, kg/m ² | 26.0 (3.0) |
| Resting SBP, mm Hg | 122.4 (12.0) |
| Resting DBP, mm Hg | 82.6 (7.6) |
| Alcohol consumption, % | |
| Abstainers | 11.6 |
| >Two drinks per day | 20.3 |
| Current smokers, % | 32.9 |
| Parental hypertension, % | 39.6 |

Values shown for age, body mass index, and BP are mean (SD). Parental hypertension includes maternal and paternal histories of hypertension.



Association between SBP and DBP responses in anticipation of exercise and 4-year incidence of high BP. REF indicates reference category in logistic regression models.

mm Hg: 22.2%; >15 mm Hg: 24.0%.) Subsequent age-adjusted models examined potential confounding by smoking, alcohol consumption, physical activity, body mass index, and positive maternal and paternal histories of hypertension. A parallel series of logistic regression models examined the association between DBPA and risk of high BP. Seven subjects with missing DBP readings before exercise were excluded from the models of DBPA. Consistent with prior research,³³ we found that resting SBP and resting DBP at baseline significantly predicted high BP at follow-up in the full KIHD study sample (OR=1.07 [95% CI, 1.06 to 1.08] and 1.16 [95% CI, 1.14 to 1.19] for an increase of 1 mm Hg in SBP and DBP, respectively). Consequently, all SBPA models were also adjusted for baseline resting SBP, and all DBPA models were adjusted for baseline resting DBP. All statistical analyses were conducted with LOGISTIC and GLM procedures from SAS,³⁴ version 6.09, installed on a Sun Sparcstation 20.

Results

Mean (±SD) SBPA was +20.2 (±14.2) mm Hg and mean (±SD) DBPA was +9.8 (±7.7) mm Hg. Both SBP and DBP responses were positively associated with age (both *P*<.0001).

In a logistic regression model, with SBPA entered as a continuous variable, SBPA significantly predicted subsequent high BP after adjusting for age and resting SBP (OR=1.03 [95% CI, 1.01 to 1.05]). Similarly, DBPA modeled continuously significantly predicted high BP at follow-up, after adjusting for age and resting DBP (OR=1.07 [95% CI, 1.03 to 1.10]).

A logistic regression model that included SBPA in approximate quartiles (<10 mm Hg; 10 to 19 mm Hg; 20 to 29 mm Hg; ≥30 mm Hg) revealed a dose-response relationship, with the most-reactive group at nearly four times the risk of having high BP at follow-up relative to the least-reactive group, after adjusting for age and resting SBP (OR=3.80 [95% CI, 1.90 to 7.63]) (see the Figure). Men in the second and third quartiles of SBPA also were at significantly increased risk of high BP compared with the nonreactors (OR=2.07 [95% CI, 1.04 to 4.11] and 2.78 [95% CI, 1.41 to 5.48], respectively). Subsequent adjustments for baseline smoking, physical activity, alcohol consumption, body mass index, and maternal and paternal histories of hypertension did not importantly affect these associations (see Table 2).

A similar pattern of findings was seen with DBPA modeled in approximate quartiles (<5 mm Hg; 5 to 9 mm Hg; 10 to 15 mm Hg; >15 mm Hg), with both the third and fourth quartiles of reactors at significantly

TABLE 2. Association Between BP Change in Anticipation of Exercise and Incidence of High BP 4 Years Later: Kuopio Ischemic Heart Disease Risk Factor Study

| | OR | 95% CI |
|-------------|----------|-----------|
| SBPA | | |
| <10 mm Hg | Referent | ... |
| 10-19 mm Hg | 2.28 | 1.12-4.63 |
| 20-29 mm Hg | 3.02 | 1.51-6.07 |
| ≥30 mm Hg | 4.13 | 2.00-8.52 |
| DBPA | | |
| <5 mm Hg | Referent | ... |
| 5-9 mm Hg | 1.52 | 0.79-2.94 |
| 10-15 mm Hg | 2.14 | 1.05-4.39 |
| >15 mm Hg | 3.43 | 1.72-6.82 |

SBPA indicates difference between seated SBP measurement before exercise and average seated resting SBP measured 1 week earlier; DBPA, difference between seated DBP measurement before exercise and average seated resting DBP measured 1 week earlier. OR values are from logistic regression models with adjustment for age, baseline resting SBP (baseline resting DBP in DBPA model), smoking, physical activity, alcohol consumption, body mass index, and maternal and paternal histories of hypertension. For SBPA analyses, n=508; DBPA, n=501. Cases of high BP, n=116.

increased risk of subsequent high BP relative to the nonreactors (OR=2.24 [95% CI, 1.11 to 4.51] and 3.65 [95% CI, 1.86 to 7.17], respectively) after adjusting for age and resting DBP (see the Figure). Controlling for baseline smoking, physical activity, alcohol consumption, body mass index, and parental hypertension did not effectively alter these relationships (see Table 2).

Although our sample of 508 did not include any men with established hypertension (BP ≥165/95 mm Hg) or taking antihypertensive medications at baseline, 25% did have a baseline resting BP in the borderline hypertensive range (SBP of 140 to 164 mm Hg and/or DBP of 90 to 94 mm Hg) and 34% reported a history of cerebrovascular stroke or coronary heart disease, including angina or previous myocardial infarction; were taking medication for cardiac insufficiency; or experienced ischemic episodes during the exercise test. Thus, to determine whether our measure of anticipatory BP reactivity would predict subsequent hypertensive status among initially disease-free men, we repeated the logistic regression models excluding the 266 men (52%) who showed borderline hypertensive pressures at rest and/or who showed evidence of coronary heart disease or cerebrovascular stroke. Although the number of men with high BP at follow-up was small in this remaining very healthy group of subjects (37 of 242 men), we did find a graded association between quartiles of anticipatory BPA at baseline and risk of high BP at follow-up. Indeed, healthy men who showed SBPA greater than or equal to 30 mm Hg or DBPA greater than 15 mm Hg were at more than five times the risk of showing hypertensive pressures at follow-up relative to the least-reactive men, after adjusting for age and resting BP (OR=5.21 [95% CI, 1.50 to 18.2] and 5.90 [95% CI, 1.58 to 22.0] for SBPA and DBPA, respectively). These associations were maintained in models that also adjusted for the other known risk factors for hypertension (Table 3).

Given that exaggerated BP responses during exercise have previously been shown to predict hypertension,¹⁻⁴ we also examined the association between BP achieved during exercise and hypertensive status at follow-up.

TABLE 3. Association Between BP Change in Anticipation of Exercise and Incidence of High BP 4 Years Later Among 242 Initially Disease-Free Participants From the Kuopio Ischemic Heart Disease Risk Factor Study

| | OR | 95% CI |
|-------------|----------|-----------|
| SBPA | | |
| <10 mm Hg | Referent | ... |
| 10-19 mm Hg | 2.89 | 0.80-10.5 |
| 20-29 mm Hg | 3.98 | 1.14-14.0 |
| ≥30 mm Hg | 5.90 | 1.58-22.0 |
| DBPA | | |
| <5 mm Hg | Referent | ... |
| 5-9 mm Hg | 2.01 | 0.53-7.59 |
| 10-15 mm Hg | 5.03 | 1.24-20.4 |
| >15 mm Hg | 5.84 | 1.42-24.0 |

SBPA indicates difference between seated SBP measurement before exercise and average seated resting SBP measured 1 week earlier; DBPA, difference between seated DBP measurement before exercise and average seated resting DBP measured 1 week earlier. OR values are from logistic regression models with adjustment for age, baseline resting SBP (baseline resting DBP in DBPA model), smoking, physical activity, alcohol consumption, body mass index, and maternal and paternal histories of hypertension. For SBPA analyses, $n=242$; for DBPA, $n=238$. Cases of high BP, $n=37$.

Consistent with prior research,^{3,35-37} an exaggerated exercise BP response was defined as SBP greater than or equal to 230 mm Hg and/or DBP greater than or equal to 110 mm Hg at any point during the exercise protocol. (The bicycle ergometer test lasted for a maximum of 14 minutes, and BP was measured every 2 minutes beginning with minute 2.) Data on BP during exercise were available for 497 subjects; of these, 154 (31%) met the criteria for exaggerated SBP and/or DBP during exercise. An age-adjusted logistic regression model showed that subjects with an exaggerated exercise response were three times more likely to have high BP at follow-up than subjects with a normal exercise response (OR=3.10 [95% CI, 2.01 to 4.78]). Given this finding, we then repeated the logistic regression analyses of SBPA and DBPA and included a dichotomous variable for exaggerated exercise BP as a covariate as well as all other risk factors. The graded associations were still apparent, with those in the highest quartiles of SBPA and/or DBPA before exercise at more than three times the risk of having hypertensive BP levels at follow-up relative to the nonreactors (OR=3.38 [95% CI, 1.59 to 7.16] and 3.17 [95% CI, 1.53 to 6.59] for SBPA and DBPA, respectively). In the SBPA model, exaggerated exercise BP was a statistically significant covariate (OR=1.87, $P=.01$); however, in the DBPA model, it was not (OR=1.34, $P=.27$).

Discussion

To the best of our knowledge, this is the first study to show an association between cardiovascular reactivity to a psychological challenge and incident hypertension or high BP in an unselected population. The fact that increasingly larger BP responses during the exercise anticipation phase were related to increasingly greater risk of hypertensive pressures in a very healthy subsample suggests that cardiovascular reactivity per se has negative consequences even in the absence of clinical disease. This observation has implications for the early detection and treatment of individuals at risk for hypertension.

Our data also demonstrate the clinical significance of the pressor response during the anticipation phase of exercise. This response is a recognized phenomenon^{5,38,39}; however, it generally has not been a focus of interest, unlike the response to exercise, in part because higher pressure levels are achieved after the initiation of exercise.⁴⁰ Priming of the cardiovascular system is beneficial in preparing for exercise, which may serve to increase performance.⁵ Our data also indicate that exaggerated BP responses during the anticipation phase of an exercise stress test, responses indicative of psychologically mediated sympathetic arousal, are a precursor of pressor dysregulation.

Moreover, we found that the risk of high BP at follow-up associated with SBPA and DBPA was not substantially diminished after exaggerated exercise BP responses were taken into account. These findings lend additional support to the reactivity hypothesis; that is, our data demonstrate that it is the sympathetic activation attendant to emotional arousal but in excess of metabolic requirements that has adverse effects on the vascular system. Such reactivity may be enhancing the hypertensive process or may be an expression of a basic tendency toward hypertension.

Sympathetic activation during the anticipation phase of exercise is manifested as an increase in cardiac output with no compensatory decrease in vascular resistance.⁵ Folkow⁴¹ has shown that the heart and blood vessels undergo structural adaptations in response to the pressure overload that accompanies chronic elevations in BP. These structural adaptations serve to maintain higher pressure levels and may contribute to a structurally induced hyperreactivity.⁴² Thus, it is biologically plausible that repeated sympathetic activation in the absence of metabolic need that leads to BP elevations beyond the normotensive range, as may occur in emotionally arousing situations, could then lead to sustained pressor increases. If the activation observed in anticipation of exercise in the present study is indicative of heightened sympathetic activation experienced by these men in response to other emotionally arousing stimuli, it is perhaps not surprising then that the risk of having high BP at follow-up increased as reactivity levels increased.

Preexercise BPA was based on just one BP reading during the anticipation phase. The consistency and strength of the observed associations as well as significant positive correlations between anticipatory BP and SBP and DBP during exercise ($r=.30$ and $r=.65$, $P<.001$) suggest that the single reading obtained during anticipation was a valid indicator of BP during that phase. It is likely that the associations observed here would have been even stronger if the random interindividual variability could have been attenuated by averaging over several BP readings. Thus, additional BP measurements during this phase would have been desirable and are recommended in order to address the stability of BP during exercise anticipation.

The majority of men in our study whose resting BP at follow-up was greater than or equal to 165/95 mm Hg were not taking antihypertensive medication at the time of their follow-up examination. Hypertensive status in our study was determined by an average of two readings over a 10-minute seated rest on one occasion. Current

recommendations are that hypertension be diagnosed only after high BP readings are obtained during at least two clinic visits⁴³; therefore, we cannot properly say that these men were diagnosed hypertensive individuals. However, a comparison of the resting SBP and DBP measured at follow-up with a 6-day average of resting SBP and DBP measured at home (via a portable, oscillometric BP monitor), which was available for 93% of our subjects, indicates that the average BP obtained during the follow-up exam was a good indicator of average daily BP among our participants ($r \cong .7$, $P < .0001$). Thus, it is likely that many of the men in our study with resting BP greater than or equal to 165/95 mm Hg at the follow-up examination would meet the criteria for diagnosed hypertension.

Our findings may not be generalizable to younger, nonwhite populations or to women; however, available data are suggestive. Matthews et al³⁰ found that Δ DBP in response to standardized psychomotor challenges was associated with higher, albeit still normotensive, resting BP 6.5 years later among white middle-aged women and men and among their teenaged sons. Also, Kasagi and colleagues²⁹ showed a higher incidence of hypertension among Japanese men and women who were systolic hyperreactors (a systolic increase of 15 mm Hg or more) to the cold pressor test, relative to normal reactors, but only among those 40 years old or older at baseline. Even though the ethnic and demographic homogeneity of our study population serves to reduce confounding effects and to increase statistical power, it will be important for future studies to test the reactivity hypothesis on more demographically varied samples.

In summary, our results support the hypothesis that cardiovascular reactivity to psychological or emotional stimuli is important in the etiology of hypertension. Moreover, our findings indicate that the risk associated with reactivity is independent of traditional risk factors for hypertension. Future research will have to determine the degree to which reactivity is specific to an individual or group or to situations as well as examine the relation between reactivity and hypertension in minority and female populations. Given the health costs of hypertension and the importance of early detection of the disorder, it appears that the sympathetic activation that accompanies emotional arousal and is manifest as exaggerated BP reactivity is a significant risk factor that has clinical relevance as an indicator of a prehypertensive state.

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