Anticipatory Blood Pressure Responses to Exercise Are Associated With Left Ventricular Mass in Finnish Men
Kuopio Ischemic Heart Disease Risk Factor Study

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Background—Exaggerated cardiovascular reactivity to psychological demands may contribute to the development of left ventricular (LV) hypertrophy. We examined the cross-sectional association between anticipatory blood pressure (BP) responses to bicycle exercise and LV mass in the Kuopio Ischemic Heart Disease Risk Factor Study, a population-based epidemiological sample.

Methods and Results—Among 876 men from 4 age cohorts (ages 42, 48, 58, and 64 years), we collected echocardiographic assessments of LV mass along with measures of BP response taken before bicycle ergometry testing. Anticipatory BP responses were positively associated with LV mass, with significant associations only among younger (age <50 years) subjects with elevated resting pressures (3-way interactions for anticipatory BP×age×resting pressure for systolic and diastolic BP, all P<0.05; for younger subjects with elevated systolic BP, P<0.01; and for younger subjects with elevated diastolic BP, P<0.001). Among these subgroups, exaggerated anticipatory BP responses (top quartile) were associated with an incremental increase in LV mass of 10% or greater, corrected for body surface area. Results remained significant after adjusting for age, education, salt consumption, and resting BP, and the pattern of findings was maintained among men with no previous history of cardiovascular disease.

Conclusions—The tendency to show exaggerated pressor responses to psychological demands may be a significant independent correlate of LV mass, especially among young men with high resting pressures. This is the first study to examine such associations in a middle-aged population sample. (Circulation. 2000;102:1394-1399.)

Key Words: cardiovascular diseases ■ epidemiology ■ exercise ■ stress

Left ventricular hypertrophy (LVH) is an important risk factor for cardiovascular morbidity and mortality,1,2 including cerebrovascular accidents,3 ventricular arrhythmia, and sudden cardiac death.4,5 The risks conferred by enlarged LV mass are independent of traditional cardiovascular risk factors6 and ventricular function.7 Although this condition is important prognostically, its determinants are not completely understood. Resting blood pressure (BP) is a modest determinant of LVH,8 as are other measures of myocardial performance,8 anthropometric variables (eg, height and body mass8–10), demographic factors (such as age, race, and sex8–11), and in some studies, sodium and alcohol consumption.12 Multivariate models including such variables, however, account for <50% of the variance.8

Hemodynamic and neuroendocrine responses to the psychological demands of daily life may explain some of the unexplained variance in LV mass. Studies of the hemodynamic determinants of LV mass have focused on the cellular and subcellular events that may link mechanical load with cellular growth,13 such as local secretion of angiotensin II and its trophic effect on LV tissue.14,15 Norepinephrine has also been implicated as a trophic hormone16–18 (also see References 19 and 20). In an experimental canine model,21 LV mass was increased by 28% after 9 weeks of repeated hindlimb compression, a manipulation that elicits a neurogenic pressor response. Results were attributed to the increased mechanical load and to the elevations in plasma norepinephrine associated with this manipulation.

Given that physiological adaptations to psychological demands may alter LV mass, individual differences in hemodynamic response during psychological challenge (“cardiovascular reactivity”) have been explored as a potential marker of LVH risk. A number of studies have shown small but significant positive associations between cardiovascular responses to psychological challenges (eg, mental arithmetic, public speaking) and LV mass.22–26 Results are not entirely

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TABLE 1. Sample Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Younger Group (Ages 42, 48 y)</th>
<th>Older Group (Ages 54, 60 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>468</td>
<td>408</td>
</tr>
<tr>
<td>Age, y</td>
<td>45.0 (3.0)</td>
<td>56.9 (3.0)</td>
</tr>
<tr>
<td>Education level*</td>
<td>2.7 (0.71)</td>
<td>2.4 (0.76)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.6 (3.3)</td>
<td>26.8 (3.1)</td>
</tr>
<tr>
<td>Resting SBP, mm Hg</td>
<td>126.6 (14.1)</td>
<td>130.4 (16.5)</td>
</tr>
<tr>
<td>Resting DBP, mm Hg</td>
<td>88.3 (10.6)</td>
<td>87.6 (10.0)</td>
</tr>
<tr>
<td>History of cardiovascular disease*</td>
<td>16.7%</td>
<td>41.8%</td>
</tr>
<tr>
<td>Medically treated hypertension</td>
<td>9.6%</td>
<td>27.9%</td>
</tr>
<tr>
<td>SBP change during exercise preparation, mm Hg</td>
<td>16.0 (12.4)</td>
<td>25.5 (15.7)</td>
</tr>
<tr>
<td>DBP change during exercise preparation, mm Hg</td>
<td>7.6 (7.9)</td>
<td>10.2 (8.4)</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise indicated.

*On a 1–4 rating scale, where 1 indicates less than primary school; 2, primary school completed; 3, more than primary school, less than high school; and 4, high school completed or more.

†Includes symptomatic coronary heart disease, asymptomatic coronary heart disease, and stroke.

consistent across studies\textsuperscript{27–29} or subgroups\textsuperscript{10,25,26}; among other factors, differences in age and health status may explain these discrepant results.

The Kuopio Ischemic Heart Disease (KIHD) Risk Factor study is a population-based investigation of risk factors for cardiovascular disease and other related outcomes in a representative sample of eastern Finnish men.\textsuperscript{30} Echocardiographic measures of LV mass were assessed at baseline in this sample, and participants also underwent a standard bicycle ergometry procedure. Because our focus was on the participants’ responses to psychological challenges, we examined measures of anticipatory BP taken before exercise onset.\textsuperscript{31}

Our goal in this report was to examine the cross-sectional association between these anticipatory BP responses and LV mass. Age and resting BP were explored as effect modifiers in this study. This is the first report to characterize the relationship between behaviorally elicited cardiovascular reactivity and echocardiographic measures of LV mass in a middle-aged population sample (in this case, men).

Methods

Subjects

The KIHD Risk Factor Study involves men from 4 age groups, 42, 48, 54, and 60 years old, who were born in the city and region of Kuopio, Finland. LV mass data were collected on those (cohort 2: N=1516, 82.6% of those eligible) who had baseline assessments between 1986 and 1989. Owing to scheduling constraints, echocardiographic data (n=984) and bicycle ergometry data (n=1305) were available on only a portion of the cohort. Ninety-two percent (902 of 984) of the echocardiographic scans were readable. In sum, both measures were available and readable in 876 participants.

Compared with the rest of cohort 2, this sample was somewhat younger (P<0.001), better educated (P<0.001), and less likely to have prevalent cardiovascular disease (28.3% versus 34.4%, P<0.001) and medically treated hypertension (18.2% versus 25.6%). Characteristics of the current study sample are presented in Table 1 by age.

Procedures

Examinations were carried out over 2 days, 1 week apart, and consisted of a number of biomedical, anthropometric, physiological, and psychosocial measurements. All subjects gave their informed consent to the testing, and the study protocol was reviewed and approved by the Institutional Ethics Committee of the University of Kuopio.

Measures

Measurement of LV Mass

Echocardiographic studies were performed with an ATL Ultramark IV system with the use of 2D-guided M-mode measurements with a 3.0- or 3.5-MHz transducer. 2D-guided M-mode images were obtained from the parasternal window and a perpendicular projection across the heart, with participants lying in a modified left lateral decubitus position. LV end-diastolic internal dimension (LVIDd), end-diastolic thickness of the interventricular septum (IVSTd), and end-diastolic thickness of the LV posterior wall (PWTd) were among the measures collected. All measures were calculated from leading edge to leading edge. The same physician (J.E.) performed the sonography and measurements. LV mass was calculated by using the Devereux formula (corrected American Society of Echocardiography cube method\textsuperscript{32–34}) shown here: LV mass in grams=0.8×1.04[(IVSTd+LVIDd+PWTd)\textsuperscript{3}−LVIDd\textsuperscript{3}]+0.6. The reproducibility of this measure was tested in a random sample of 30 subjects reexamined at a 3-week interval, yielding a test-retest reliability of 0.82.

LV mass measures are typically adjusted for body surface area (BSA)\textsuperscript{34} or height\textsuperscript{35}. We used both approaches for this study. Distributions for each were logarithmically transformed to correct for skewness. Both types of adjustments yielded comparable results; therefore, only BSA-corrected measures are presented.

Resting BP and Anticipatory BP Response

Two resting BP assessments were obtained during a seated rest period (at minutes 5 and 10) and the readings were averaged. One week later, an additional BP assessment was recorded 5 minutes after subjects were seated on a bicycle ergometer and just before the start of an exercise test protocol. A trained observer used a random-zero muddler sphygmomanometer (Hawksley) for all BP measures. All measurements were conducted during the morning hours.

Anticipatory systolic (SBP) and diastolic (DBP) responses were calculated as the difference between the anticipatory exercise BP and the mean resting BP from the first examination day. The preparatory phase of exercise is associated with centrally mediated changes in autonomic and cardiovascular activity that mimic those associated with exercise performance.\textsuperscript{36,37} In this sample, measures of anticipatory BP change have been shown to predict 4-year increases in resting BP as well as carotid disease progression.\textsuperscript{31,38,39}

Other Assessments

Medical history and medication use were recorded during an initial medical examination. Education was coded 1 through 4 (see Table 1). Physical activity (total activity duration) was measured with a 12-month leisure-time history modified for this population.\textsuperscript{40,41} Average weekly alcohol consumption (g/wk) was assessed by administering a questionnaire (quantity-frequency method) from the Scandinavian Drinking Survey.\textsuperscript{42–44} Average sodium consumption was measured on the basis of responses to a 4-day food record administered by a nutritionist.\textsuperscript{44} This was also logaritmically transformed to correct for skewness. Body mass index (BMI) was assessed as [(weight in kg)/(height in m\textsuperscript{2})] and BSA (g/m\textsuperscript{2}) as [(weight in kg)\textsuperscript{2.7}}×(height in m\textsuperscript{2})\textsuperscript{0.007184}].

Measures of exercise-related BP response were derived for each subject by subtracting mean seated baseline (first examination day) from a manual manometry reading taken during exercise performance (8 minutes into testing). These data were available for only a portion of the sample. We previously examined stress-related cardiovascular reactivity in this sample by using a series of standardized mental tasks.\textsuperscript{45,46} These mental task measures were administered at.

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Data Analysis

Measures of LV mass were regressed on measures of anticipatory BP response by using a general linear models procedure (PROC GLM). Separate models were run for SBP and DBP responses. Age cohort (ages 42, 48, 54, or 60 years) and resting BP (SBP for SBP reactivity and DBP for DBP reactivity) were used as covariates in all of the models. In follow-up analyses, other potential risk factors were explored as covariates.

In addition to their effects as covariates, the effects of age (<50 or ≥50 years) and resting BP were explored as effect modifiers. Cross-product terms were used to test for 2-way and 3-way interactions in each model, with adjustments for relevant main effects and lower-level interactions as appropriate.

Results

Associations Between LV Mass and Reactivity

As hypothesized, anticipatory BP reactivity was positively associated with LV mass (for SBP response [n=876], b=0.001, P<0.05; for DBP response [n=867], b=0.002, P=0.06). Each of these associations was modified, however, by significant 3-way interactions with age and resting pressure (all P<0.05). To explore the pattern of these interaction effects, we examined separately the older and younger subjects (age >50 or <50 years) and those with resting pressures at or above versus below the median for SBP (median=126 mm Hg) or DBP (median=88 mm Hg). The associations were significant only among younger subjects with elevated resting BP (for younger subjects with elevated SBP [n=224], b for anticipatory SBP response=0.003, P<0.01; for younger subjects with elevated DBP [n=231], b for anticipatory DBP response=0.007, P<0.001) but not among younger subjects with lower BP or among older subjects.

Magnitude and Patterning of Effects

Figures 1A and 1B illustrate the associations between anticipatory BP responses (by quartile) and LV mass in the sample as a whole. Age and resting BPs were included as covariates. Figures 1C and 1D illustrate these same associations among younger individuals with elevated pressures. Measures are presented here in original (BSA-adjusted) units rather than logarithmically transformed values.

Among younger subjects with elevated resting pressures, those with exaggerated (top quartile, >26 mm Hg) SBP responses during exercise anticipation showed a 10% incre-
ment in LV mass when compared with the least responsive quartile, and those with exaggerated (top quartile, >10 mm Hg) DBP responses showed a 13% increment in LV mass. By polynomial regression, these data were not consistent with a curvilinear (quadratic or cubic) function. When we examined linear effects by quartile, however (ie, dummy codes with the bottom quartile as the reference), we found that LV mass was significantly larger only for the top quarter of the SBP reactors (P<0.05). The top 2 quarters of DBP responders each showed elevated LV mass (P<0.05) relative to the reference group.

Covariate Analyses
We examined a series of confounders that might account for these observed relationships, including education (as an index of social status), BMI, habitual alcohol consumption, self-reported physical activity, salt consumption, exercise-related BP response, and measures of resting BP (SBP or DBP). As shown in Table 2, 3 of these variables showed significant relationships with the predictor (anticipatory BP responses) and the criterion (LV mass) measures at P<0.10; these were education, sodium consumption, and resting pressures. LV mass was regressed on anticipatory BP response along with these 3 covariates. The major findings remained significant (for 3-way interactions, all P<0.05 and <0.01 for SBP and DBP responses, respectively; for associations within young subjects with elevated pressures, all P<0.05 and <0.001 for SBP and DBP responses, respectively).

Eighteen percent of the sample reported using antihypertensive medications, with a larger proportion of these in the older half of the sample (P<0.01; see Table 1). Those taking antihypertensive medications had significantly larger LV mass compared with unmedicated subjects (P<0.001), consistent with a probable history of hypertension in the former group. We examined medication use (dummy coded) as an additional covariate in the sample as a whole and in the younger group with elevated pressures. The original patterns of relationships remained unaltered.

Finally, we examined the associations separately among individuals without a history of cardiovascular disease (no coronary heart disease, stroke, or antihypertensive treatment, n=567: 204 older and 363 younger subjects). Within this smaller sample, the 3-way interactions were no longer significant, but the reactivity–LV mass associations were significant among younger subjects with elevated pressures, as before (for SBP response, n=167, b=0.003, P<0.05; for DBP response, n=165, b=0.008, P<0.001).

Discussion
BP responses during exercise anticipation are significantly associated with LV mass among eastern Finnish men. These associations are independent of other risk factors for LV mass, such as resting BP and sodium consumption. The relationships were limited to younger men (<50 years of age) with elevated resting pressures; within this group, the effects were approximately linear but were heightened among those showing the most exaggerated responses.

Causal explanations for the findings cannot be resolved with these cross-sectional data. Repeated behaviorally evoked BP responses may exert a cumulative impact on the work load of the ventricle, contributing to enhanced LV mass among highly reactive individuals. On the other hand, elevated LV mass may also contribute to increased reactivity. For example, to the extent that LVH impairs ventricular filling, it may trigger a compensatory pattern of accentuated peripheral vascular and noradrenergic responses, consistent with the present results.

If behaviorally elicited cardiovascular reactivity is assumed to play a causal role, several plausible mechanisms might be invoked. Stress-related BP fluctuations may act as a mechanical stimulus to the myocytes, activating protein synthesis and hypertrophy. This process may be mediated by angiotensin II synthesis in cardiac tissue. Cardiac sympathetic nervous activity may also affect myocyte development. These potential mechanisms remain to be explored.

The association between anticipatory BP and LV mass was limited to younger individuals in this sample (age <50 years), and the effects were enhanced in the presence of elevated resting pressures. If LV mass reflects the cumulative influence of pressor effects with time, we might expect exaggerated BP responses during behavioral demands to exert their greatest impact among those with high resting pressures. It is possible that anticipatory BP responses may be less reliable among older individuals, given their higher prevalence of heart disease and medication use. It is also possible that the cardiovascular effects of aging (including increases in vascular stiffness and pulse pressure) could reduce the relative importance of anticipatory BP response as a determinant of LV mass. In any case, it should be noted that we have previously shown a similar pattern of age-related differences when we examined the association between stress-
related cardiovascular reactivity and carotid atherosclerosis in this sample.46

There is some prior evidence linking behaviorally evoked cardiovascular reactivity and LV mass, but the findings have been inconsistent across studies and samples. Current results suggest that this association may vary systematically as a function of sample characteristics, with both age and resting pressure playing an important role in moderating these effects. The extent to which such results may be validly generalized to samples that are at lower risk for disease or to samples that are more demographically heterogeneous than this one (with respect to sex, race, and ethnicity) remains to be determined.

This is the first study to examine the association between cardiovascular responsiveness to behavioral challenge and echocardiographic measures of LV mass in an adult population sample. Results are roughly consistent with our previous findings in this population, in which we have shown that behaviorally evoked cardiovascular responses may be correlated, both cross-sectionally and prospectively, with the development of hypertension31 and carotid atherosclerosis.3,8,39 Further prospective investigation is needed to examine behaviorally elicited reactivity as a predictor of changes in elevated LV mass and to examine the implications of such findings for predicting clinical end points. Further work is needed, as well, to help us understand the mechanisms by which age and hypertension may modify the associations shown herein.

Acknowledgments

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