Hemodynamic Predictors of Incident Hypertension
The Framingham Heart Study
Wendy S. Post, Martin G. Larson, Daniel Levy

Abstract Previous reports indicate that cardiac output is increased early in the course of hypertension. The purpose of this study was to identify with echocardiography hemodynamic features in normotensive adults that predicted the development of hypertension. Framingham Heart Study subjects were eligible for this investigation if they were normotensive at the baseline examination (systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg, and no antihypertensive medications) and if they were free of coronary heart disease, congestive heart failure, valvular heart disease, atrial fibrillation, hypertrophic cardiomyopathy, diabetes mellitus, and renal insufficiency. The study included 1118 men (mean age, 44 years) and 1559 women (mean age, 46 years). After 4 years of follow-up of this normotensive cohort, 201 men (18.0%) and 257 women (16.5%) had developed hypertension. In separate, age-adjusted multivariable logistic regression analyses, increased cardiac index (men: odds ratio=1.19 for one standard deviation increment, P=0.03; women: odds ratio=1.17, P=0.02) and end-systolic wall stress (men: odds ratio=1.24, P=0.06; women: odds ratio=1.43, P<0.001) were related to the development of hypertension in both sexes. In addition, increased heart rate in men (odds ratio=1.25, P=0.006) was a significant predictor of hypertension. After adjustment for age and baseline blood pressure, none of the hemodynamic variables was a significant predictor of hypertension. In addition, load-independent indexes of contractility revealed only a minimally greater proportion of subjects with increased contractility at baseline in the group that developed hypertension compared with those who remained normotensive. The present study revealed a hemodynamic profile in the preclinical stage of hypertension in age-adjusted analyses that was similar to the hyperkinetic circulatory phase found in the early stage of hypertension in some previous studies; however, after controlling for age and baseline blood pressure, none of the hemodynamic parameters were significant predictors of the development of hypertension. Knowledge of an individual’s hemodynamic profile does not improve the prediction of hypertension risk that can be obtained from baseline blood pressure and age alone. Further studies are warranted to investigate hemodynamic features in various stages of hypertension after adjustment for age and blood pressure.

Methods

Subjects
The Framingham Heart Study is a prospective epidemiologic study established in 1948 to evaluate potential risk factors for coronary heart disease. The original cohort included 5209 men and women, aged 28 to 62 years, who were residents of Framingham, Mass. In 1971, 5135 additional subjects were entered into the Framingham Offspring Study. Study design and selection criteria have been published.9-11 All study subjects gave informed consent, and this study was approved by an institutional review board.

Subjects for the present study were original Framingham Heart Study participants who attended biennial examination 16 (1979 through 1981) and Offspring Study subjects who attended their second examination (1979 through 1983). Subjects were excluded if they met any of the following criteria: (1) systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg, (2) use of antihypertensive medication, (3) coronary heart disease or congestive heart failure, (4) valvular heart disease, (5) atrial fibrillation, (6) diabetes mellitus, (7) renal insufficiency (creatinine >2.0 mg/dL), (8) hypertrophic cardiomyopathy, (9) age younger than 20 years, or (10) an inadequate echocardiogram.

At the index examination, body height and weight measurements, medical history, physical examination, serum creatinine,
fasting glucose, electrocardiography, and echocardiography were obtained routinely. Body mass index (calculated as weight [in kilograms] divided by the square of height [in meters]) was used as a measure of obesity. A physician measured two resting systolic and diastolic blood pressures at the first and fifth Korotkoff phases. Systolic and diastolic blood pressures were determined by means of these two measurements. Heart rate was obtained during echocardiography. The diagnoses of coronary heart disease and congestive heart failure were established by a committee of three physicians who evaluated records from the Framingham Heart Study clinic, inpatient hospitalizations, and visits to outside physicians in accordance with published criteria. Diabetes was defined as a fasting blood glucose level greater than or equal to 7.77 mmol/L (140 mg/dL), a random nonfasting blood glucose level greater than or equal to 11.11 mmol/L (200 mg/dL), or the use of insulin or an oral hypoglycemic agent. The diagnosis of valvular heart disease was based on clinical examination evidence of a systolic murmur of intensity graded greater than or equal to 3 on a six-point scale or any diastolic murmur.

**Echocardiographic Methods**

Standard M-mode echocardiographic techniques were used in this study as previously described. Measurements of left ventricular internal dimension (LVID) and posterior wall thickness (PWT) were made in accordance with methods outlined by the American Society of Echocardiography. Left ventricular volumes were estimated with the Teichholz regression equations: end-diastolic volume (EDV)=7.0(LVIDx4.9+PWT); ejection fraction (EF)=EDV/ESV. Stroke volume (SV)=EDV−ESV. The following formulas were used to calculate hemodynamic variables: mean arterial pressure=diastolic blood pressure (BP)+[(systolic BP−diastolic BP)/3]; fractional shortening=(LVID−LVID−LVID−stroke/LVIDx100); stroke volume index (SVI)=SV/body surface area (BSA); cardiac output (CO)=SV×heart rate; cardiac index (CI)=CO/BSA; and total peripheral resistance=(mean arterial pressure×80)/CO. End-systolic wall stress (ESWS) was estimated using a catheterization-verified formula: ESWS=0.334xLVIDxstrokex systolic BP/[PWT−strokex(1+PWT−stroke/LVID−stroke)].

**Follow-up**

Four years after the index examination, subjects returned for a follow-up examination that included blood pressure measurements. In accordance with the criteria of the Fifth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure, incident hypertension was defined as systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure greater than or equal to 90 mm Hg (mean of two readings), or current use of antihypertensive medications. Subjects who developed coronary heart disease or congestive heart failure during follow-up were excluded because of the potential antihypertensive effects of pharmacological therapies for these disease entities.

**Statistical Methods**

All analyses were done separately for men and women. Group means and standard deviations were used to summarize baseline clinical variables. Linear regression was used to adjust baseline hemodynamic variables for age. Each hemodynamic variable was assessed separately by means of unadjusted, age-adjusted, and systolic and diastolic blood pressure-adjusted analyses. Results are summarized by odds ratio (OR), 95% confidence interval, and probability value. For continuous variables, the OR is expressed for a one standard deviation increment. An association was deemed to be statistically significant at a value of P<0.05.

Subjects who developed hypertension were compared with those who remained normotensive with regard to measures of contractility. In subjects who remained normotensive at follow-up, a linear regression model was fitted relating fractional shortening to log end-systolic wall stress. The percentages of subjects who fell outside the 95% individual prediction intervals (fitted value±1.96×root-mean-square error) were compared between the subjects who remained normotensive and the subjects who were hypertensive at follow-up. A scatterplot was generated for subjects who were hypertensive at follow-up and was superimposed on the linear regression lines generated from the subjects who were normotensive at follow-up. All analyses were done on a Sparstation 2 (SUN Microsystems) using the Statistical Analysis System (SAS).

**Results**

Subjects

The study sample was derived from 2805 men and 3413 women who attended the index examination. There were 1111 men and 1314 women excluded because of hypertension at the baseline examination, and 140 men and 79 women excluded because of coronary heart disease, congestive heart failure, or valvular heart disease. An additional 82 men and 45 women had atrial fibrillation, diabetes mellitus, renal insufficiency, age less than 20 years, or hypertrophic cardiomyopathy. An inadequate echocardiogram resulted in the exclusion of 173 men and 178 women. There were 1299 men and 1797 women eligible for this study. During follow-up, 181 men and 238 women died, developed either coronary heart disease or congestive heart failure, or did not attend the follow-up examination. Therefore, the study sample included 1118 men and 1559 women, 86.1% and 86.8%, respectively, of eligible individuals.

**Clinical and Echocardiographic Characteristics**

At the baseline examination, subjects ranged in age from 20 to 88 years, with a mean age (±SD) of 44±12 years for men and 46±12 years for women. Mean systolic blood pressure was 120±10 mm Hg in men and 115±12 mm Hg in women; corresponding diastolic values were 77±7 and 73±7 mm Hg.

At the follow-up examination 4 years later, 201 men (18.0%) and 257 women (16.5%) were hypertensive. Subjects with hypertension were older than subjects who remained normotensive (51±13 versus 43±12 years in men, and 53±12 versus 44±12 years in women). They also had higher baseline blood pressure (systolic blood pressure 126±9 versus 118±10 mm Hg in men, 125±11 versus 113±11 mm Hg in women; diastolic blood pressure 81±6 versus 76±7 mm Hg in men, 77±8 versus 72±7 mm Hg in women).

At the baseline examination, age-adjusted mean heart rate, cardiac index, total peripheral resistance, and end-systolic wall stress were slightly higher in men and women who developed hypertension compared with those who remained normotensive (Table 1).

**Progression to Hypertension**

The ability of hemodynamic variables to predict the development of hypertension, without adjustment for
age and baseline blood pressure, was analyzed with simple logistic regression (Table 2). Cardiac index (OR=1.16 for a one standard deviation increment, \(P<.05\)) and heart rate (OR=1.26, \(P=.003\)) were significant predictors of incident hypertension in men. In women, total peripheral resistance (OR=1.25, \(P=.001\)) and end-systolic wall stress (OR=1.20, \(P=.008\)) were associated with the development of hypertension.

Subsequently, the analyses were adjusted for age by use of multivariable logistic regression (Table 2). Increased cardiac index (men: OR=1.19, \(P=.03\); women: OR=1.17, \(P=.02\)) and end-systolic wall stress (men: OR=1.24, \(P=.006\); women: OR=1.43, \(<.001\)) were associated with incident hypertension in both sexes. In addition, increased heart rate (OR=1.25, \(P=.006\)) was a significant predictor of the development of hypertension in men but not in women. Total peripheral resistance was not a significant predictor of incident hypertension in women after adjustment for age. After adjustment for baseline systolic and diastolic blood pressures, in addition to age, none of the hemodynamic variables was a predictor of incident hypertension.

There was a significant trend toward an increased incidence of hypertension during follow-up when subjects were grouped into age-adjusted quartiles of cardiac index (Fig 1). Similar trends were observed for subjects grouped into quartiles of age-adjusted end-systolic wall stress and for quartiles of heart rate in men. When subjects were further stratified into quartiles of baseline systolic blood pressure, there were no significant associations between hemodynamic variables and the development of hypertension. The data for cardiac index, ad-

<table>
<thead>
<tr>
<th>Table 1. Hemodynamic Characteristics of Subjects at Baseline According to Hypertension Status at Follow-up, Age-Adjusted</th>
</tr>
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<tbody>
<tr>
<td><strong>Baseline Hemodynamic Characteristic</strong></td>
</tr>
<tr>
<td>Normotensive at Follow-up</td>
</tr>
<tr>
<td>(n=917)</td>
</tr>
<tr>
<td>HR, bpm</td>
</tr>
<tr>
<td>FS, %</td>
</tr>
<tr>
<td>SVI, mL/m²</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
</tr>
<tr>
<td>TPR, dyne·s/cm⁵</td>
</tr>
<tr>
<td>ESWS, 10³ dyne/cm²</td>
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HR indicates heart rate; FS, fractional shortening; SVI, stroke volume index; CI, cardiac index; TPR, total peripheral resistance; and ESWS, end-systolic wall stress. Values are mean±SEM.

<table>
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<tr>
<th>Table 2. Odds Ratios for Progression to Hypertension Based on Hemodynamic Variables</th>
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<tbody>
<tr>
<td><strong>Sex and Variable</strong></td>
</tr>
<tr>
<td><strong>Men</strong></td>
</tr>
<tr>
<td>HR 10 bpm</td>
</tr>
<tr>
<td>FS 4%</td>
</tr>
<tr>
<td>SVI 6 mL/m²</td>
</tr>
<tr>
<td>CI 0.5 L·min⁻¹·m⁻²</td>
</tr>
<tr>
<td>TPR 293 dyne·s/cm⁵</td>
</tr>
<tr>
<td>ESWS 13×10³ dyne/cm²</td>
</tr>
<tr>
<td><strong>Women</strong></td>
</tr>
<tr>
<td>HR 10 bpm</td>
</tr>
<tr>
<td>FS 4%</td>
</tr>
<tr>
<td>SVI 6 mL/m²</td>
</tr>
<tr>
<td>CI 0.5 L·min⁻¹·m⁻²</td>
</tr>
<tr>
<td>TPR 344 dyne·s/cm²</td>
</tr>
<tr>
<td>ESWS 12×10³ dyne/cm²</td>
</tr>
</tbody>
</table>

Definitions are as in Table 1 and SBP, systolic blood pressure; DBP, diastolic blood pressure; and OR, odds ratio.

*Incremental unit for each echocardiographic variable is one standard deviation.

Results of separate multivariable logistic regression models for each echocardiographic variable.
Baseline Cardiac Index Quartile

FIG 1. Bar graph shows age-adjusted incidence of hypertension by quartiles of cardiac index. Trend test: P=.02 for both men and women separately. Shown are cardiac index quartile 1 (mean=2.04 L·min⁻¹·m⁻² for men, 2.10 L·min⁻¹·m⁻² for women), quartile 2 (2.47 L·min⁻¹·m⁻² for men, 2.53 L·min⁻¹·m⁻² for women), quartile 3 (2.77 L·min⁻¹·m⁻² for men, 2.83 L·min⁻¹·m⁻² for women), and quartile 4 (3.35 L·min⁻¹·m⁻² for men, 3.45 L·min⁻¹·m⁻² for women).

Baseline Systolic Blood Pressure Quartile

FIG 2. Bar graphs show the incidence of hypertension with subjects grouped by quartiles of cardiac index and stratified by quartiles of systolic blood pressure. Trend test: P=.45 for men, P=.33 for women. Shown are systolic blood pressure quartile 1 (mean=107 mm Hg for men, 100 mm Hg for women), quartile 2 (116 mm Hg for men, 110 mm Hg for women), quartile 3 (123 mm Hg for men, 118 mm Hg for women), and quartile 4 (132 mm Hg for men, 130 mm Hg for women).

Baseline End Systolic Wall Stress

FIG 3. Graphs show linear regression of fractional shortening vs log end-systolic wall stress for subjects who remained normotensive at follow-up with a superimposed scatterplot of subjects who were hypertensive at follow-up. Dotted lines represent 95% individual prediction intervals. Each square represents one or more subjects who were hypertensive at the follow-up examination (r=-.66 in men, r=-.62 in women).

Discussion

Cardiac index and end-systolic wall stress were significant predictors of incident hypertension in age-adjusted analyses; however, after adjustment for age and baseline blood pressure, none of the hemodynamic variables was significantly associated with the incidence of hypertension. Knowledge of an individual's hemodynamic profile does not improve the prediction of hypertension risk that can be obtained from baseline blood pressure and age alone. Although there have been reports of hemodynamic features in various stages of hypertension,5-7,25-28 there have been no previous population-based reports of hemodynamic predictors of the development of hypertension in adults.

Previous longitudinal studies have shown that cardiac index is increased early in hypertension and that during follow-up cardiac index falls and peripheral resistance increases.5-7 The Bergen Long-term Study on Central Adjusted for age and stratified according to baseline systolic blood pressure, are presented in Fig 2.

Contractility

Since left ventricular function depends on loading conditions, contractility of the heart must be assessed with measures that are relatively unaffected by loading conditions. We used linear regression to describe the relation between baseline end-systolic wall stress and fractional shortening in subjects who were normotensive at follow-up. This method incorporates afterload conditions by using end-systolic wall stress; it is also considered to be largely independent of preload.21-24 There was a negative correlation between fractional shortening and log end-systolic wall stress (men: r=-.66, P<.0001 in men; women: r=-.62, P<.0001 in women). In the group that was normotensive at follow-up, 2.6% of men and 2.5% of women fell above the upper bound of the 95% individual prediction interval, and 2.5% of men and 2.6% of women fell below the lower bound. When data points for subjects who were hypertensive at follow-up were superimposed on the intervals generated from the normotensive subjects, 4.5% of men and 3.9% of women fell above and 2.5% of men and 1.6% of women fell below the 95% bounds (Fig 3). This reflects only a minimally greater proportion of individuals with increased contractility at baseline in the group that developed hypertension.

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Cross-sectional investigations using echocardiography have found increased contractility in a subset of hypertensive subjects compared with normotensive control subjects.25-28 Since left ventricular mass has been shown to be a predictor of hypertension in several longitudinal studies,1,4 we hypothesized that an increase in left ventricular mass before the development of hypertension may lead to an increase in contractility that promotes hypertension. However, in our study sample, load-independent indexes of contractility revealed only a minimally greater proportion of individuals with increased contractility at baseline in the group that developed hypertension during follow-up compared with those subjects who remained normotensive. It is possible that the discrepancy between our results and those of previous studies may be due to a smaller difference in baseline blood pressures between our two groups than between the groups studied previously. We found that after adjustment for baseline systolic blood pressure in the group that developed hypertension there was a further decrement in the number of subjects who exhibited evidence of increased contractility before the development of hypertension.

An important strength of this study is the well-characterized history obtained from subjects through many years of follow-up and review of medical records. This information allowed us to select subjects who were free of clinically apparent cardiovascular disease, which can alter hemodynamic measurements. In addition, the relatively large number of subjects in the study who developed hypertension allowed more precise estimation of the risk of hypertension and permitted adjustment for age and baseline blood pressure.

A limitation to our study was the estimation of hemodynamic parameters using M-mode echocardiographic measurements rather than two-dimensional echocardiography or invasive hemodynamic measurements. However, since subjects with coronary heart disease were excluded, errors in volume calculations resulting from left ventricular geometric distortions were minimized. In addition, the noninvasive formula for end-systolic wall stress and the volume equations have been validated through catheterization and angiography.15,16 Noninvasive measurements may reflect the resting hemodynamic state more accurately, whereas angiographic monitoring is affected by alterations in sympathetic activity associated with the procedure. It is also not practical to perform angiography on large numbers of subjects because of its associated morbidity and expense. Another limitation to this study is that the subjects in the Framingham Heart Study are predominantly white; these results may not apply to other ethnic or racial groups.

In summary, increased cardiac index and end-systolic wall stress were significant predictors of the development of hypertension in age-adjusted models; however, these relations were no longer significant after adjustment for age and baseline blood pressure. Further studies are warranted to investigate hemodynamic features in various stages of hypertension after controlling for age and baseline blood pressure. Although there is an association between increased left ventricular mass and greater risk for the development of hypertension, hemodynamic parameters did not contribute to the prediction of hypertension after age and baseline blood pressure were taken into account.

References
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