Evidence for Additional Blood Pressure Correlates in Adults 20–56 Years Old

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SUMMARY The offspring of parents belonging to the original Framingham Heart Study cohort, and spouses of these offspring, were examined beginning in 1971. Cardiovascular examinations similar to those performed on the parents in 1952–1953 were given to offspring and their spouses. The mean blood pressure (BP) appeared to be lower in the female offspring-spouses than in the cohort mothers. Comparable multivariate analyses on 3588 offspring and spouses of both sexes, ages 20–49 years, and 1842 parents, ages 30–49 years, confirmed the frequently reported importance of weight, heart rate, alcohol consumption, glucose and hematoctrit or hemoglobin as independent positive correlates and smoking as an inverse correlate of both systolic and diastolic BP. In the offspring-spouse population, the additional measured variables of total serum proteins and plasma triglycerides added significantly to prediction of BP in both sex groups, and a less striking negative association was found for serum phosphorus. The findings for serum proteins and triglycerides were supported in a separate population of middle-aged twin men. Even with the additional measured variables, only 28–34% of the total BP variance is explained in these populations.

EPIDEMIOLOGIC APPROACHES to the understanding of the “mosaic” causation of hypertension have usually taken the form of cross-sectional studies that investigate possible associations between measured variables and blood pressure (BP) in available populations.1–8 The conclusions about the correlates of BP have been remarkably similar among these studies, which have identified weight, heart rate, glucose, alcohol consumption, hematocrit or hemoglobin and smoking as BP correlates.

Because hypertension seems to have its roots at an early age, evaluation of correlational data from younger adult populations may allow a better understanding of the determinants of interindividual variability in BP. The pathologic complications resulting from BP elevation or the aging process itself are not yet expressed in such populations. Further, in older populations, elimination of a sizeable subpopulation, such as patients on antihypertensive therapy, may be necessary to avoid the effects of treatment on the variables being studied.

The Framingham Study provides a unique opportunity to compare BP correlates and interrelationships in two generations, with offspring and parents being examined at a relatively young age and in a similar manner but approximately 20 years apart. Because the offspring and their spouses were examined recently, more extensive studies were done than at the time of the parents’ examination. The availability of a battery of clinical chemistries allowed possible identification of new BP-related variables besides those previously identified in the parents.

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Methods

Populations

In the original Framingham Heart Study cohort of 5209 persons ages 30–62 years there were 1644 pairs of spouses.9 Of these, 1404 couples were known to have at least one child and 1202 of these families (86%) were represented by one child or more in the Framingham Offspring Study. The 1202 mothers gave birth to 3717 children, of whom 2656 (71%) were examined. The spouses of 1212 of these offspring were studied as well. The potential impact of nonresponse was evaluated by determining that the disease experience and the risk factors were similar in the parents of examined and unexamined offspring. The second-generation offspring-spouse population used in this analysis consists of the 1705 men and 1883 women who had values for all variables and were ages 20–49 years when examined for the first time between 1971 and 1975.

The parent generation includes 858 men and 984 women, ages 30–49 years when examined in 1952–1953, who had the designated measurements. In addition, between 1969 and 1973, as part of the NHLBI Twin Study, 105 pairs of male twins ages 42–56 years were examined in Framingham and an additional 409 pairs of twins were examined elsewhere in the United States according to a similar protocol.10 Four hundred sixty pairs of twins have the necessary data for this analysis.

Procedures

The offspring participants were seen after an overnight fast and were asked not to smoke on the morning of the examination. The duration of fasting was confirmed by interview but compliance with nonsmoking was not. The sequence of the examination followed the protocol established for the twelfth biennial examination of the parents. A nurse first measured height and weight using a standard beam balance, and then determined systolic blood pressure (SBP) and
fifth-phase diastolic blood pressure (DBP) to the nearest 2 mm Hg on the right arm using the appropriate sized cuff with the participants seated. A history form was completed by the physician with the participant sitting for about 30 minutes. Then, using the same protocol used by the nurse, the physician took another BP, which was used for all analyses. While participants were fasting, blood was drawn, promptly separated and the plasma sent to the laboratory for lipoprotein analysis using the techniques described in the Lipid Research Clinics Laboratory Manual. Serum and anticoagulated blood were sent to the Framingham Union Hospital, where standard methods and quality control procedures were used for SMA 12/60 determinations and hematograms.

The parents had been similarly examined 20 years previously at the second biennial examination, except blood was drawn in the nonfasting state and more limited laboratory studies were performed. Cholesterol was measured by the Abel-Kendall method, and the heart rate was measured from a pulse reading rather than from the ECG.

The common protocol for the twin study was modeled after the Framingham cohort examination. As with the parents and offspring, BP was measured first by a nurse and then by a physician using a standard sphygmomanometer. The participant was seated and first- and fifth-phase BPs were recorded. The physician's values for all twins were used for the analyses. In the twins, as in the offspring-spouses, triglycerides and other lipoproteins were determined on fasting specimens according to laboratory methods similar to those used in the Lipid Research Clinics Program. Glucose levels were measured by a blood specimen drawn 1 hour after a 50-g glucose load. Clinical chemistries included in the SMA 12/60 profile were determined on fasting specimens. A smoking history was taken, weight and height were measured using a standard beam balance and the heart rate was determined from the ECG.

**Multiple Regression Analysis**

A step-up multivariate regression analysis program was used to test for significant associations with BP in parents and offspring-spouses. This procedure considers the entire list of independent variables and first enters the variable with the highest simple correlation with BP. Independent variables are added sequentially using the partial correlation with BP, after control for independent variables already in the equation, as the selection criterion. When no further independent variables have significant \( p < 0.05 \) partial correlations with BP, the selection stops. Twenty-two factors were used in the multivariate analysis of the offspring-spouse group, including high- and low-density lipoprotein cholesterol, triglycerides, height, Quetelet's index, subcapular skinfolds, weight, heart rate from the ECG, current cigarette smoking (yes or no), usual number of alcoholic drinks per week, age in years, vital capacity in liters, hematocrit, red blood count, white blood count, total serum proteins, uric acid, fasting plasma glucose, calcium, phosphorus, BUN, total bilirubin, alkaline phosphatase, LDH and SGOT.

For the parent group age, weight, heart rate, cholesterol, hemoglobin, uric acid, nonfasting glucose, smoking, and alcohol consumption histories were available from the time of the second examination. There were fewer unknown values at this examination than at the previous one. The square of the multiple correlation coefficient (R), which measures the proportion of BP variation "explained" by the independent variables, is computed for the final step of each analysis.

For the twin population, with its inherent pairwise correlation, the mean BP for each pair of twins was used in the regression analysis. A step-down multiple regression procedure using the factors found to be significant in the offspring-spouse population was used. This approach was used to attempt confirmation of the same identified BP correlates in the separate twin population.

The partial regression coefficients in the various tables were standardized by multiplying each original coefficient by the ratio of the variable's standard deviation over the BP standard deviation. This adjustment allows a comparison of the relative strength of the association between the variables and BP in each analysis. Because population characteristics and variables differed, the standardized regression coefficients are not strictly comparable between the tables. The rank of coefficients within analyses is provided to facilitate comparisons of the importance of particular variables between tables.

**Results**

The mean BPs by age and the number of subjects in the two generations of family members are shown in table 1. The female offspring-spouses have lower SBPs, with differences of 4–7 mm Hg. The BP differences between fathers and male offspring-spouses are somewhat smaller.

Tables 2 and 3 list standardized regression coefficients for the multivariate regression analyses in the parents and offspring-spouses for variables that are available in both groups and significantly related to SBP or DBP in men or women. The rank of the variables in the tables corresponds to that of their entry in the regression and thus reflects the approximate order of importance of the variables as BP correlates.

Weight and heart rate are consistent major correlates for SBP and DBP in men and women of both generations. Age has an important role in both parents and offspring-spouses. The relative rank of uric acid, cholesterol and alcohol consumption is similar in both generations and cigarette smoking has a negative sign in all groups. The coefficient for fasting glucose in offspring-spouses is higher than for casual blood sugar in the parents. In both generations, weight, hematocrit or hemoglobin, smoking and cholesterol generally have higher coefficients for DBP than for SBP. The
regression coefficients for age in women are somewhat greater than for men and, overall, the multiple R is higher in women than in men for both generations. Finally, using the same array of correlates in two generations, the multiple R values are greater in each case for offspring-spouses than for parents.

In table 4 the addition of total serum proteins, triglycerides and phosphorus for the offspring has the effect of eliminating uric acid and cholesterol from the original regression equations and raising the overall multiple R value. Total serum proteins are slightly better correlates in men than women and are ranked among the top four. The coefficients for phosphorus are persistently negative and slightly larger for women than for men.

The importance of total serum proteins as a BP correlate was confirmed in a separate population of middle-aged twin men. Table 5 shows that total serum proteins rank third for both SBP and DBP. Triglycerides were significant for DBP but not for SBP.

The negative coefficient for phosphorus was not significant in either case, but phosphorus was the last variable to be eliminated from the SBP regression equation.

**Discussion**

Interpretation of any BP differences between parents and their offspring are complicated by several factors; however, the lower values for women, at least, appear to be real. Second-generation males and females have lower BPs than parents (table 1), but these values are not controlled for differences in obesity or medical management of hypertension. To complicate the interpretation, a rather major decline in BP was observed over the first three biennial examinations of the parents. Because the offspring-spouses have been examined only once, we do not know whether a similar decline will occur. When the

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**Table 1. Age- and Sex-Specific Mean Blood Pressures in Framingham Parents and Offspring-Spouses**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mothers (n = 984)</td>
<td>SBP (mm Hg)</td>
<td>DBP (mm Hg)</td>
<td>SBP (mm Hg)</td>
</tr>
<tr>
<td>Female offspring-spouses (n = 1883)</td>
<td>SBP (mm Hg)</td>
<td>114.5 (n = 711)</td>
<td>121.4 (n = 596)</td>
</tr>
<tr>
<td>Fathers (n = 858)</td>
<td>SBP (mm Hg)</td>
<td>126.8 (n = 302)</td>
<td>130.4 (n = 556)</td>
</tr>
<tr>
<td>Male offspring-spouses (n = 1705)</td>
<td>SBP (mm Hg)</td>
<td>124.7 (n = 673)</td>
<td>126.9 (n = 563)</td>
</tr>
</tbody>
</table>

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure.

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**Table 2. Standardized Partial Regression Coefficients for Systolic and Diastolic Blood Pressures in Framingham Parents Ages 20-49 Years, and Significant (5% Level) Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.187(1)</td>
<td>0.247(1)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.172(2)</td>
<td>0.157(2)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.115(3)</td>
<td>0.068(8)</td>
</tr>
<tr>
<td>Age</td>
<td>0.090(4)</td>
<td>0.105(5)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.075(5)</td>
<td>0.084(7)</td>
</tr>
<tr>
<td>Hemoglobin or hematocrit</td>
<td>0.127(3)</td>
<td>0.062(8)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>-0.111(4)</td>
<td>-0.108(4)</td>
</tr>
<tr>
<td>Glucose</td>
<td>-0.078(5)</td>
<td>-0.078(5)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.068(6)</td>
<td>0.065(7)</td>
</tr>
<tr>
<td>Multiple R</td>
<td>0.346</td>
<td>0.432</td>
</tr>
</tbody>
</table>

Rank of coefficient is given in parentheses.

**Table 3. Standardized Partial Regression Coefficients for Systolic and Diastolic Blood Pressures in Framingham Offspring-Spouses Ages 20-49 Years, and Significant (5% Level) Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.229(2)</td>
<td>0.283(1)</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.272(1)</td>
<td>0.208(2)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.075(7)</td>
<td>0.070(7)</td>
</tr>
<tr>
<td>Age</td>
<td>0.072(8)</td>
<td>0.168(3)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-0.105(9)</td>
<td>0.053(9)</td>
</tr>
<tr>
<td>Hemoglobin or hematocrit</td>
<td>0.104(4)</td>
<td>0.142(4)</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>-0.088(6)</td>
<td>-0.107(5)</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.091(5)</td>
<td>0.063(8)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.108(3)</td>
<td>0.091(6)</td>
</tr>
<tr>
<td>Multiple R</td>
<td>0.501</td>
<td>0.536</td>
</tr>
</tbody>
</table>

Rank of coefficient is given in parentheses.

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure.
first examination values are compared, BP in daughters is significantly lower than in mothers, even after adjustment for hypertensive medication, age, and weight differences.\textsuperscript{12} To maintain better comparability, the present analyses used BPs and correlates from the parent's second biennial examination.

Analyses in three interrelated populations provide the basis for conclusions concerning BP and certain correlates. All three populations show the often-reported major relationship between weight and BP.\textsuperscript{13-17} Heart rate is another important correlate in the offspring-spouses and parents, but not in the twins. This relationship with BP has also been reported.\textsuperscript{18, 19} The method of measurement does not seem to be important, because heart rate was determined from the ECG in the offspring-spouses and from the resting pulse in the parents.

A relationship between glucose and BP has been described.\textsuperscript{2, 20} Whether the glucose is fasting, as in the offspring-spouses, or casual, as in the parents, only a modest association exists. In the twin population, the postload glucose is the most significant correlate, surpassing even weight. Such a strong relationship between a “challenged” glucose value and BP was seen also in the Thousand Aviator Study, with the simple correlation coefficient for fasting glucose and BP being about 0.020–0.041, but the 2-hour postprandial value correlating with an $r$ value of 0.148–0.196.\textsuperscript{21}

The slight relationship between alcohol and BP in these populations has been shown in other studies.\textsuperscript{18, 22, 23} Inconsistencies may be due to the notoriously inaccurate methods for measuring alcohol consumption or to differing levels of alcohol consumption. A threshold effect of 2–3 drinks per day for the association with BP to occur has been postulated, although this does not seem to be the case in the offspring-spouse population.

Cigarette smoking is a consistently negative correlate for DBP in the three populations. An Israeli study showed an apparent prospective positive relationship between hypertension and smoking,\textsuperscript{18} as did a study from Chicago.\textsuperscript{24} The acute effects of smoking on the cardiovascular system as mediated by local catecholamine release are well described.\textsuperscript{25} Perhaps the regular smoker who does not smoke before and during the examination experiences a downward rebound of BP due to the short-term absence of a nicotine stimulus.

Total serum proteins, triglycerides and, to a lesser extent, hematocrit or hemoglobin and phosphorus, are independently related to BP in these populations. These modest associations might suggest that the measured variables are only indirect indicators of some other more fundamental BP relationship, perhaps involving blood volume. If one postulates a
decreasing blood volume with increasing BP, it is possible to explain the correlational findings involving these variables.

Low plasma volume has been a frequent finding in many investigations of hypertensive patients, and an inverse relationship between BP and blood volume was found in men with DBPs greater than 105 mm Hg. In a Scandinavian community screening project, the total protein concentration for men newly identified as hypertensive (SBP greater than 100 mm Hg) was 7.29 mg% compared with 7.03 mg% in the remainder of the population. The same relationship was found in a smaller subsample that was being exercised. During acute exercise, protein increased slightly in the two groups, suggesting a decrease in fluid volume associated with the exercise-related increase in BP.

The mechanism for the increased total protein concentration in hypertensive patients is believed to be secondary to elevated DBP, causing increased hydrostatic pressure with transudation of fluid into the extravascular space. Lessening the resulting increase in protein concentration, however, is a tendency toward increased transcapillary escape of albumin in hypertensive patients.

Hematocrit or hemoglobin is positively and independently associated with DBP in parents and offspring spouses, and less strongly so with SBP. In the previously mentioned Scandinavian study, hematocrit was significantly higher in hypertensive subjects defined by elevated DBP than in normal persons both at rest and with exercise. In Evans County and in the Chicago Board of Health Community Survey, a similar higher correlation between hematocrit and DBP than SBP was found. Decreased blood volume probably accounts for the association between hematocrit and BP. Consistent with this hypothesis is the observation that after patients with essential hypertension and so-called stress or relative polycythemia due to decreased blood volume had been treated with antihypertensive medication, their plasma volumes expanded to normal and hematocrit decreased.

Multivariate analysis in this offspring-spouse population revealed a slight but significant relationship of BP with triglycerides but no independent relationship with total, high-density or low-density lipoprotein cholesterol. Other investigators have found an absent or weakly positive univariate relationship between cholesterol level and BP. A similar multivariate cholesterol relationship is present in the parents for both SBP and DBP. The twins provide an additional opportunity to examine the triglyceride relationship to BP. When differences in BP level for monozygotic twins from the NHLBI Twin Study were analyzed for differences in other variables, triglycerides explained part of the remaining environmental variance. The multivariate analysis for DBP in the twins confirms a relationship between triglyceride and BP.

The relationship between triglyceride and BP could also be secondary to decreased blood volume. With changes in blood volume due to different postures, triglycerides as well as cholesterol increase acutely with decreased blood volume. We do not know if such a relationship between BP, triglyceride and blood volume would persist chronically.

A definite but modest inverse relationship between BP and serum phosphorus was found for offspring women, and a similar but less definite relationship was found in men. In the twins, phosphorus was related inversely to SBP but not significantly. This observation is consistent with a recent report that showed an inverse relationship between phosphorus and SBP in middle-aged men. Those authors suggest that increasing BP level might cause a decreased reabsorption of phosphorus in the proximal tubules of the kidney.

The interactions between the variables, especially hematocrit, total serum proteins, triglycerides, serum phosphorus and BP, and the relationship with blood volume, are probably more complex than can be easily elucidated in a general population survey. For example, observed relationships could also be explained by the more complicated hypothesis that a subgroup in the population has a slightly expanded blood volume. An appropriate blend of people, some with increased and others with decreased blood volume, in a population could result in the relationships described in this epidemiologic study.

This interpretation would be more consistent with the popular notion that increased extracellular fluid is a precursor of hypertension. A sequence of an early increased blood volume and cardiac output followed by increased peripheral resistance and normal or reduced volume has been postulated. However, Dushman et al. were able to identify only a small subgroup who had increased blood volume among subjects with modest hypertension. In terms of the inverse phosphorus-BP findings, it has been determined in hypertensive patients, at least, that increased phosphaturia occurs with volume expansion from infusion of isotonic sodium chloride. Perhaps in a subgroup with increased salt intake or salt retention due to oral contraceptive use, a slightly increased plasma volume could result. As the kidney attempts to compensate for the larger salt load, a secondarily increased phosphate excretion might occur. Without actual blood volume data in the populations, clarification of these interrelationships is not possible.

Except for weight, heart rate and, perhaps, total serum proteins, the standardized regression coefficients for other factors and BP are quite modest; however, in the aggregate, the significant correlates explain 10–34% of the variability. Although a multiple R as high as 0.53–0.58 is larger than that found in most other studies, the challenge of finding new potential risk factors for elevated BP remains. When parent’s BP measured 20 years previously was added as an independent predictor of offspring’s present BP along with the already described correlates, an independent parental effect was evident. Although this association may represent a genetic influence on BP, such an effect could be mediated by some as yet undescribed environmental factors.

Mechanisms not related to blood volume should be investigated to explain these findings. Perhaps total
serum proteins, triglycerides or hematocrit are related directly to BP level or to some unidentified independent factor. A univariate correlation between serum proteins and SPB has been described in a West African tribe. This association was attributed to a third factor that might lower both proteins and BP, such as infection or malnutrition. Mathews et al. have drawn attention to the increased frequency of certain classes of globulins in hypertensive patients and have postulated a possible autoimmune etiology for BP elevation.

Cross-sectional epidemiologic studies can suggest alternate research directions for smaller clinical studies or animal experiments that might elucidate the complicated interrelationships of BP and the measured variables. The associations of BP with total serum proteins, phosphorus and triglycerides described in this study could provide such a stimulus.

References

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