Risk Factors for Arterial Hypertension in Adults With Initial Optimal Blood Pressure

The Strong Heart Study

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Abstract—Whether metabolic factors and their change over time influence development of arterial hypertension in adults with initially optimal blood pressure (BP) is unknown. We analyzed associations of BP in the optimal range (<120/80 mm Hg), metabolic risk factors, and their changes over 4-year follow-up, with 8-year incident hypertension, in a cohort of American Indians with a high prevalence of obesity. At baseline, 967 participants with optimal BP and no prevalent cardiovascular disease (69.5% women; mean age, 54±7 years) were evaluated and reexamined after 4 (second examination) and 8 years to evaluate predictors of 8-year incident arterial hypertension. In participants with normal glucose tolerance, baseline BP and decrease in high-density lipoprotein cholesterol from baseline to the second examination were the most potent predictors of 8-year arterial hypertension (both $P<0.0001$), with additional effects of baseline waist circumference and its increase, increase in BP, and presence of diabetes at the second examination (all $P<0.04$). In participants with impaired glucose tolerance or diabetes, the most potent predictor of 8-year incident hypertension was diabetes at the second examination ($P<0.0001$) followed by a increase in BP and LDL cholesterol over the first 4 years (both $P<0.001$). Thus, incident arterial hypertension can be predicted by initial metabolic profile and unfavorable metabolic variations over time, in addition to initial BP. At optimal levels of initial BP, increasing abdominal obesity, and abnormal lipid profile are major predictors of development of arterial hypertension. Possible implications of these findings for primary cardiovascular prevention should be tested in prospective studies. **(*Hypertension*. 2006;47:162-167.)**

Key Words: metabolism ■ insulin resistance ■ lipids ■ lipoproteins ■ population ■ risk factors

Arterial hypertension is the most prevalent cardiovascular risk factor in most populations, and as much as 26% and 28% of incident cardiovascular disease in men and women, respectively, is primarily attributable to arterial hypertension.[1] The cumulative lifetime risk of developing hypertension was calculated to approach 90% in the Framingham Heart Study cohort.[2] Thus, there is increasing evidence that efforts should be devoted to preventing development of arterial hypertension, although debate continues about which blood pressure (BP) values should be considered abnormal.[3–6] There is substantial evidence that overweight obesity and nonoptimal BP are potent predictors of definite hypertension in populations,[7–9] although mechanisms relating obesity to hypertension are still to be clarified.[9] Socioeconomic status also influences the incidence of arterial hypertension.[10] How initial optimal BP and body weight status interact with other metabolic factors and their change over time in predicting the development of arterial hypertension has received little attention despite evidence that obesity induces multiple cardiovascular risk factors, the clustering of which comprises the metabolic syndrome.[11] Thus, we analyzed metabolic predictors of incident arterial hypertension in the American-Indian participants of the Strong Heart Study (SHS) with initial optimal BP, including the initial level of BP as a predictor variable.

Methods

Population

The SHS is a population-based longitudinal cohort study of cardiovascular risk factors and disease in American Indians from 3 communities in Arizona, 7 in Southwestern Oklahoma, and 3 in South Dakota and North Dakota, as extensively described.[12–16] Participants seen during the baseline examination, in 1989 to 1992, with available information on body size and fat distribution, diabetes status, lipid profile, and BP, were selected for the present analysis. Exclusion criteria included systolic pressure ≥120 mm Hg, diastolic pressure ≥80 mm Hg, ongoing antihypertensive treatment,[4,5,17] and prevalent and/or incident nonfatal cardiovascular disease over 8-year

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follow-up through the third SHS examination. Prevalent and incident cardiovascular disease were adjudicated as reported previously in detail[15,18] by physician members of the SHS Mortality and Morbidity Committees to confirm causes of death and to establish specific cardiovascular disease diagnoses.

Diabetic and obese participants were included; participants with fasting triglyceride levels >750 mg/dL were excluded. Thus, 967 normotensive participants (69.5% women) with a mean age of 54±7 years were finally considered in the present analysis.

Laboratory Tests and Classification of Participants

Fasting plasma glucose and lipid profiles were measured by standard methods.[14] Diabetes and impaired glucose tolerance were diagnosed by 1997 American Diabetes Association recommendations.[19] Obesity was classified based on the 1998 National Institutes of Health guidelines,[20] and the same guidelines were used to define sex-specific central fat distribution.

Statistical Analysis

Data were analyzed using SPSS 12.0 software (SPSS). Data are expressed as mean±SD. Indicator variables were included for the 3 field centers: Arizona, South/North Dakota, and Oklahoma. Incident hypertension was defined as BP ≥140 and/or 90 mm Hg or ongoing antihypertensive treatment at both second and third exams after 46±9 and 92±13 months from baseline examination, respectively. Descriptive statistics were obtained by 1-factor ANOVA or χ^2 distribution. When needed, the REGW-F post hoc test was also carried out. Predictors of arterial hypertension were evaluated using binary multiple logistic regression and a backward stepwise procedure, with P-to-enter <0.05 and P-to-remove >0.1, which are the default values of the SPSS statistical package. Participants with impaired glucose tolerance or diabetes were pooled and analyzed separately from subjects with normal glucose tolerance based on considerations developed in the exploratory ANOVA. Wald statistics were used to estimate the strength of the estimated relative risk (expressed as the exponential of the b coefficient). Variables considered in logistic models were grouped in 2 subsets: the first one was used to predict incident hypertension at the second examination and included baseline age, gender, field center, body mass index (BMI), waist girth, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, systolic and diastolic BP, plasma glucose, and diabetes status. The second set of variables was added to the first set for prediction of incident hypertension at the third examination and comprised prevalent hypertension and diabetes at the second examination and the percentage changes of systolic and diastolic BP; body weight; fasting glucose; total, HDL, and LDL cholesterol; triglycerides; and waist girth between the first and second examination.

Results

At the first SHS examination, 36.3% of participants were overweight (62.4% women), and 25.9% (76.8% women) had class I, 11.5% (80.2% women) had class II, and 5.6% (81.5% women) had class III obesity. Central fat distribution was detected in 68.1% of participants (84.2% women). Diabetes was present in 30.6% of participants (74.1% women) and impaired glucose tolerance in 15.9% (70.2% women).

Table 1 shows baseline characteristics of participants remaining normotensive over the 8 years of follow-up compared with the separate groups that developed arterial hypertension at the second or third examination. Analysis for trend showed that, at baseline, subjects developing arterial hypertension were more obese and had more central fat distribution, higher BP, high plasma glucose, and greater prevalence of diabetes (all P<0.001). Post hoc comparison revealed no difference between subjects with identified hypertension at 4 or 8 years.

TABLE 1. Baseline Characteristics of Participants With Persistent Normal Pressure or Incident Hypertension

Baseline Characteristics	Remaining Normotensive (n=692)	Hypertension After 4 Years (n=113)	Hypertension After 8 Years (n=162)
Age (y)	53.88±7.15	54.34±7.16	53.81±6.84
BMI (kg/m^2)†	29.00±5.60	31.29±6.68	31.26±6.07
Waist girth (cm)†	100.20±14.13	106.42±15.15	105.99±15.25
Sex (% women)	65.9%	74.1%	70.2%
Body weight classification†			
Normal (<25 kg/m^2)	23.4%	12.4%	15.4%
Overweight (25 to 29.9 kg/m^2)	38.6%	32.4%	30.2%
Class I obesity (30 to 34.9 kg/m^2)	23.6%	35.4%	29.0%
Class II obesity (35 to 39.9 kg/m^2)	10.1%	14.2%	15.4%
Class III obesity (mtequ]40 kg/m^2)	4.3%	7.1%	9.9%
Central fat distribution (%)†	63.6%	80.5%	70.2%
Systolic BP (mm Hg)†	108.67±7.62	112.35±7.30	111.88±6.72
Diastolic BP (mm Hg)*	69.21±6.61	70.91±6.27	70.50±6.40
Fasting plasma glucose (mg/dL)†	130.66±65.68	154.22±85.19	160.34±90.26
Diabetes (%)†	25.5	43.2	43.4
HDL cholesterol (mg/dL)	46.50±12.74	44.57±11.32	45.83±12.70
LDL cholesterol (mg/dL)	109.10±31.03	104.94±28.71	108.78±31.01
Total cholesterol (mg/dL)	188.87±37.27	184.28±35.89	190.49±38.24
Triglycerides (mg/dL)	122.81±72.97	134.79±84.48	133.23±71.50

For central fat distribution, waist circumference >88 cm in women or >102 cm in men.
*P for trend <0.001.
†P for trend <0.0001.

TABLE 2. Baseline Characteristics of Participants With Normal BP by Glucose Tolerance Status

Baseline Characteristics	Normal GT (n=517)	Impaired GT (n=154)	Diabetes (n=296)
Age (y)	53.70±7.37	54.40±7.11	54.09±6.58
BMI (kg/m^2)†	28.09±5.27	31.25±6.02	31.48±6.08
Waist girth (cm)†	97.33±13.62	105.66±13.61	108.03±14.36
Sex (% women)†	65.9%	70.2%	74.1%
Body weight classification†			
Normal (<25 kg/m^2)	28.7%	10.6%	12.8%
Overweight (25 to 29.9 kg/m^2)	39.0%	33.1%	32.4%
Class I obesity (30 to 34.9 kg/m^2)	20.9%	33.8%	31.0%
Class II obesity (35 to 39.9 kg/m^2)	9.1%	13.9%	14.8%
Class III obesity (≥40 kg/m^2)	2.4%	8.6%	9.0%
Central fat distribution (%)†	56.9%	77.5%	83.1%
Systolic blood pressure (mm Hg)	109.15±7.69	109.94±7.47	110.19±7.52
Diastolic blood pressure (mm Hg)	69.26±6.48	70.06±6.85	69.87±6.60
Fasting plasma glucose (mg/dL)†	96.61±8.15	116.42±4.41	224.12±84.45
HDL cholesterol (mg/dL)†	48.17±13.36	45.66±12.06	42.85±10.87
LDL cholesterol (mg/dL)†	111.72±31.19	110.44±31.40	101.64±28.80
Total cholesterol (mg/dL)*	191.83±36.63	189.95±37.04	181.57±37.59
Triglycerides (mg/dL)†	113.02±60.66	132.34±78.62	145.06±88.35
ATP III metabolic syndrome†	15.7%	82.8%	89.0%

GT indicates glucose tolerance.
*P for trend <0.001.
†P for trend <0.0001.

Characteristics of this cohort were also examined on the basis of glucose metabolism. Table 2 shows that, at baseline, participants with either impaired glucose tolerance or diabetes exhibited a greater prevalence of central obesity, with somewhat lower plasma cholesterol, as well as HDL and LDL cholesterol, and no difference in baseline BP. The prevalence of women was also greater in the presence of impaired glucose metabolism. Post hoc comparison, however, did not demonstrate any statistically appreciable difference between subjects with impaired glucose tolerance or diabetes.

Based on the above exploratory analysis suggesting that the population subgroups with impaired glucose tolerance or diabetes could be considered a quite homogeneous cluster for the purpose of the present analysis, the study population was divided into 2 groups, normal glucose tolerance and impaired glucose tolerance/diabetes, and the following analyses were performed separately in these 2 subgroups.

Predictors of Hypertension After 4 Years

After 4 years, even with initially optimal levels of BP, development of arterial hypertension (n=113) was associated with higher baseline systolic pressure (b=0.077/mm Hg; P<0.004) and BMI (b=0.059/kg×m^{-2}; P<0.05) in normal glucose tolerance and with higher baseline systolic BP (b=0.048/mm Hg; P<0.03) and diabetes status (b=0.68; P=0.05) in impaired glucose tolerance/diabetes without any other considered variable (listed in the Statistical Analysis section) remaining in the final predictive models.

Predictors of Hypertension After 8 Years

In participants with normal baseline glucose tolerance, as well as stringently normal BP, higher baseline waist circumference and systolic BP, evidence of diabetes at the second examination, increase in systolic BP and waist circumference, and decrease in HDL cholesterol from baseline to the second examination predicted 8-year arterial hypertension independent of the development of definite hypertension at the second examination (4 years) (Table 3). Of note, the 4-year decrease in HDL cholesterol was as strong an independent predictor of 8-year incident hypertension as the baseline level of systolic BP, as shown by the respective Wald statistics.

In contrast, a slightly different profile of predictors of 8-year incident arterial hypertension was observed in participants with impaired glucose tolerance or diabetes at baseline (Table 4). The most potent independent predictor of incident hypertension was the presence of diabetes at the time of the second examination followed by the increase in systolic BP and in LDL cholesterol over time, with a small additional contribution from the baseline level of systolic BP.

Discussion

Previous studies have shown that the incidence of arterial hypertension depends on the initial BP level. The Framingham Heart Study reported that hypertension incidence over 4 years rose from 5% with optimal BP to 37% with high-normal pressure in individuals below age 65 and from 16% to 50% in older adults.[21] Obesity and weight gain also contributed to the progression to hypertension, leading the Framing-

TABLE 3. Independent Predictors of Incident Arterial Hypertension After 8 Years in SHS Participants With Baseline BP <120/80 mm Hg and Normal Glucose Tolerance

Variables in the Model	*b*	Wald	*P* Value (≤)	Exp(B)	95% CI for Exp(B) Lower	Upper
Waist circumference (cm)	0.026	5.07	0.02	1.026	1.003	1.050
Systolic BP (mm Hg)	0.092	14.74	0.0001	1.096	1.046	1.148
Hypertension after 4 years (1=no; 2=yes)	0.732	2.80	0.095	2.079	0.881	4.904
Diabetes at the second exam (1=no; 2=yes)	0.948	4.72	0.03	2.581	1.097	6.073
Change in systolic BP from baseline to second exam (%)	0.030	4.25	0.04	1.031	1.001	1.060
Change in HDL cholesterol from baseline to second exam (%)	−0.028	12.86	0.0001	0.972	0.957	0.987
Change in waist circumference from baseline to second exam (%)	0.044	5.29	0.02	1.045	1.007	1.085

Variable entered at the first step of regression modeling: age, gender, field center, BMI, waist girth, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic BP, plasma glucose, and diabetes status at the first and second exam; percentage changes between first and second exam of systolic and diastolic BP, body weight, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and waist girth.

ham investigators to highlight the importance of weight control for primary prevention of hypertension. High relative body weight is a consistent predictor of incident hypertension across populations. In the Nijmegen Cohort Study,[22] weight gain and baseline diastolic BP were the strongest predictors of 18-year incident diastolic hypertension. The Coronary Artery Risk Development in (Young) Adults study[23] reported that the 10-year incident hypertension over 10 years in 5115 black and white young adults was most strongly predicted by age and initial systolic BP, with additional independent contributions from BMI; waist circumference; physical activity; alcohol intake; pulse rate; cigarette smoking; education; and levels of fasting insulin, triglycerides, uric acid, and HDL cholesterol. More recently, Borghi et al[24] compared 15-year incidence of stable diastolic hypertension in 70 adults with high-normal BP[4] and elevated or normal cholesterol levels and found that hypercholesterolemia was associated with higher incidence of hypertension after adjusting for age, initial BP, family history of hypertension, and BMI.

In contrast with the previous studies, the present analysis has been carried out considering only participants with strictly defined normal BP by Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure criteria.[5] The strategy was decided to verify whether the ability of metabolic risk factors to predict incident arterial hypertension was predominant in the context of optimal BP but relatively high prevalence of other cardiovascular risk factors. We found, in fact, a substantial impact of metabolic profile in predicting arterial hypertension.

The scenario emerging from our findings is that, in the presence of initial relatively low BP (Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure normal), the metabolic profile and its worsening over time are strong predictors of development of arterial hypertension. These findings, therefore, suggest that when BP is low, atherogenic risk factors play major roles in stiffening arteries and increasing peripheral resistance. In the presence of normal glucose metabolism, the combined effect of initial central fat distribution, increasing abdominal adiposity, and worsening of lipid profile was even greater than initial levels of systolic BP and its increase over time in predicting incident 8-year arterial hypertension. Of interest, in participants with abnormal initial glucose metabolism, evidence of diabetes at the second examination was the most potent predictor and, together with worsening in the lipid profile, explains most incident hypertension. These metabolic effects were also independent of the presence of hypertension at 4-year examination, consistent with the evidence of rapid stiffening of the arterial system exposed to diabetes.[25]

Another interesting point emerging from our findings concerns obesity. Although obesity is prevalent in the SHS population, once lipid profile and plasma glucose were

TABLE 4. Independent Predictors of Incident Arterial Hypertension After 8 Years in SHS Participants With Baseline BP <120/80 mm Hg and Impaired Glucose Tolerance or Diabetes

Variables in the Model	*b*	Wald	*P* Value (≤)	Exp(B)	95% CI for EXP(B) Lower	Upper
Sex (1=male; 2=female)	0.545	2.87	0.09	1.725	0.918	3.241
Systolic blood pressure (mm Hg)	0.062	9.67	0.002	1.064	1.023	1.107
Hypertension after 4 years (1=no; 2=yes)	1.371	10.65	0.001	3.941	1.730	8.978
Diabetes at the second exam (1=no; 2=yes)	1.517	20.00	0.0001	4.558	2.344	8.860
Change in systolic BP from baseline to second exam (%)	0.043	11.56	0.001	1.043	1.018	1.069
Change in LDL cholesterol from baseline to second exam (%)	0.009	5.361	0.02	1.009	1.001	1.017

Variable entered at the 1st step of regression modeling: age, gender, field center, BMI, waist girth, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic BP, plasma glucose and diabetes status at the first and second exam; percentage changes between first and second exam of systolic and diastolic BP, body weight, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and waist girth.

considered, body weight had less effect than expected from reports from other populations, whereas central fat distribution appears to be important only when glucose tolerance is normal (see Table 3). This different effect of central fat distribution might be attributable to the higher variability shown among participants with normal plasma glucose than among those with abnormal glucose metabolism, in whom central adiposity was almost always present. A number of investigators attribute the negative cardiovascular consequences of obesity to its association with a cluster of risk factors, rather than to its being a primary causal cardiovascular risk factor.[26] Of note, obesity is reported to be a direct causal risk factor for increasing the metabolic predictors[11] that we have identified as risk factors for incident arterial hypertension in the present study. In addition, there is previous evidence that the risk of obesity is substantially related to the accumulation of intraabdominal fat.[27,28] Overall, our results suggest that impaired glucose metabolism, abnormal lipid profile, and high-normal BP levels largely mediate the effect of central obesity in predicting incident hypertension. However, our findings also suggest that consideration of metabolic syndrome as a clinical entity might help identify individuals at risk for the development of arterial hypertension. Efforts to prevent arterial hypertension might be successful with interventions to improve body build and metabolic profile, targeted to individuals with optimal BP.

In addition to the factors highlighted in our analysis, smoking habit has also been reported to be another potential predictor of hypertension in different ethnic groups,[29] possibly because of increased arterial stiffness. Because our analyses were conducted in a population of American Indians, their generalizability needs to be verified in other populations, especially because algorithms for risk prediction are substantially affected by prevalence and distribution of individual risk factors.[30] Moreover, arterial hypertension in this population is mainly systolic,[31] and, therefore, additional study is needed to examine predictors of diastolic hypertension. It should also be considered, however, that data from this population have been repeatedly shown to be valuable in understanding metabolic phenomena associated with obesity, insulin resistance, and diabetes relevant to other populations in which these disorders are becoming epidemic.

Conclusions

Incident arterial hypertension can be predicted and potentially prevented by paying attention to initial metabolic profile and unfavorable variations therein over time, at least as strongly as by initial BP. Among individuals with initially optimal baseline levels of BP, abdominal obesity and abnormal lipid profile play major roles in the development of arterial hypertension.

Perspectives

There are implications of these findings for primary cardiovascular prevention that should be tested in prospective studies. Hypertension is the leading risk factor for cardiovascular mortality and morbidity, and much effort is devoted to reducing BP with high financial and social costs and a relative ineffectiveness of interventions, because only a relatively small proportion of the hypertensive population is optimally controlled.[32,33] Interventions to prevent this most important risk factor might be very effective in helping to reduce cardiovascular risk and direct and indirect costs related to arterial hypertension. Although the evidence that BP levels predict future high BP is neither new nor surprising, it is clear that individual detection of optimal values of BP does not allow the prediction of development of hypertension. Thus, consideration of the additional factors highlighted in this study might be crucial in setting programs focused on primary prevention of arterial hypertension.

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