Office Pulse Pressure Is a Predictor of Favorable Outcome in Young- to Middle-Aged Subjects With Stage 1 Hypertension

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Abstract—The role of pulse pressure in young individuals remains controversial. The aim of the present study was to investigate the clinical significance of elevated pulse pressure in young- to middle-aged subjects screened for stage 1 hypertension. We examined 1241 subjects (mean age, 33.1±8.4 years) from the HARVEST (Hypertension Ambulatory Recording Venetia Study), during a median follow-up of 12.1 years. To evaluate the predictive value of pulse pressure and mean blood pressure for future hypertension needing treatment and for cardiovascular events, participants were grouped into pressure tertiles. Significant determinants of pulse pressure were male sex (P=0.029), younger age (P<0.001), physical activity (P=0.003), heart rate (P<0.001), systolic white-coat effect (P<0.001), and stroke volume (n=829; P<0.001). During follow-up, 65.1% of participants developed hypertension requiring pharmacological treatment and 5.1% experienced a cardiovascular event. Participants in the highest pulse pressure tertile had a reduced risk of incident hypertension compared with those of the bottom tertile (hazard ratio, 0.75; 95% confidence interval, 0.62–0.91; P=0.003). In contrast, participants in the top mean blood pressure tertile had an increase in risk (1.91; 1.57–2.33; P<0.001). In addition, participants in the highest pulse pressure tertile had a reduced risk of cardiovascular events (0.35; 0.17–0.73; P=0.005) and those in the top mean blood pressure tertile had an increase in risk (3.06; 1.32–7.09; P=0.009). Our data show that in subjects <45 years, only mean blood pressure is a predictor of adverse outcome whereas high pulse pressure even carries a reduced risk. **(*Hypertension*. 2017;70:537-542. DOI: 10.1161/HYPERTENSIONAHA.117.09516.)** ● **Online Data Supplement**

Key Words: adolescent ■ blood pressure ■ cardiovascular events ■ hypertension ■ risk

The role of elevated pulse pressure (PP) as a risk factor for cardiovascular disease was recognized in the ESH-ESC 2013 guidelines (European Society of Hypertension/European Society of Cardiology), where it was included among the indexes of asymptomatic organ damage.[1] A high PP was defined as a PP >60 mm Hg, but this definition only applies to elderly subjects. In elderly individuals, elevated PP was demonstrated to be associated with increased risk of cardiovascular mortality,[2] stroke,[3] and recently also of cognitive decline.[4] However, an elevated PP often associated with isolated systolic hypertension (ISH) may be found also among young individuals, particularly in men, as documented by several studies.[5–8] The clinical significance of these conditions in youth is still controversial for the obvious necessity of a long-term follow-up to accumulate a sufficient number of hard end points. The first authors who highlighted a different prognostic value of PP according to age were Sesso et al.[9] Considering both PP and mean blood pressure (MBP) in the same multivariable survival model, these authors observed that in a general male population, PP had an important predictive capacity for cardiovascular disease only among people aged ≥60 years, whereas among people aged <60 years, PP only had a marginal predictive value. In a more recent study, Yano et al[10] compared the predictive value of different hypertension subtypes in a population of 18- to 49-year-old subjects free of antihypertensive treatment and observed that men with ISH had a lower risk of cardiovascular mortality than men with isolated diastolic hypertension or systolic-diastolic hypertension. To our knowledge, the predictive capacity of PP for cardiovascular disease has never been investigated in young people with hypertension. Thus, the aim of the present study was to assess the prognostic significance of elevated PP among young- to middle-aged, stage 1 hypertensives from the HARVEST (Hypertension Ambulatory Recording Venetia Study).

Methods

For the present analysis, we investigated 1241 subjects from the HARVEST, a long-term prospective cohort study, initiated in 1990 and involving 17 centers in the North East of Italy.[11–13] Only subjects who had at least 6 months of follow-up were included. Patients' recruitment was obtained with the collaboration of the local general practitioners who were instructed during local meetings. Patients

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enrolled were 18- to 45-year-old subjects, screened for stage 1 hypertension, who had never been treated for hypertension before. Subjects at high cardiovascular risk including heavy smokers (>20 cigarettes/d) and subjects with total cholesterol > 240 mg/dL were excluded. Mean age±SD at the baseline was 33.1±8.4 years, and mean systolic/diastolic BP were 145.6±10.4/94.0±6.2 mm Hg. In all study participants, the presence of diabetes mellitus, renal impairment, and cardiac diseases were excluded at the baseline.[11–13]

Procedures

The procedures followed were in accordance with institutional guidelines. Baseline data included a medical and family history and a self-compiled questionnaire about lifestyle habits: current use of coffee and alcoholic beverages, smoking status, and physical activity habits.[11–13] Other details are reported in the online-only Data Supplement. Brachial office BP at entry was the mean of 6 measurements obtained with a mercury sphygmomanometer with appropriately sized cuffs, during 2 visits performed 2 weeks apart. At the enrollment, patients underwent also 24-hour BP and heart rate monitoring, using the A&D TM2420 model 7 (A&D, Tokyo, Japan) or ICR Spacelabs 90207 monitor (Spacelabs, Redmond, WA) devices. Both of these devices were validated previously[14,15] and were shown to provide comparable results.[16] Stroke volume (SV) was measured with m-mode echocardiography in 827 subjects using the previously published procedures.[17] The study was approved by the HARVEST Ethics Committee and by the Ethics Committee of the University of Padova. A written informed consent was given by the participants.

Follow-Up

Follow-up visits were scheduled after 1, 2, 3, and 6 months and thereafter at 6-month intervals. At the beginning, all subjects were given general information about nonpharmacological measures by the HARVEST investigators, following the suggestions of current guidelines on the management of hypertensive patients. If after at least 6 months of implementation of nonpharmacological measures, the participant's BP was still above the operational threshold level, the patient was rescheduled for a visit within 2 to 4 weeks and the average BP was calculated. If BP was still above the limit, the patient was given antihypertensive drug treatment, otherwise he or she was checked at monthly intervals. The BP operational threshold level was established on the basis of the criteria adopted by international guidelines at the time of patients' evaluation (online-only Data Supplement). Then treated and untreated subjects continued to be checked at 6-month intervals. For survivors who were lost to follow-up, the data obtained at the last available visit were taken into account. Survival time for the participants was defined as the period from the date of the first visit of the participant to the date of first event.

Major Adverse Cardiovascular Events

We ascertained vital status and the incidence of fatal and nonfatal events from medical records and interviews with attending physicians and patient's families. Other details on follow-up procedures in the HARVEST were reported elsewhere.[11–13,18] Cardiovascular events included fatal and nonfatal ST-segment–elevated acute myocardial infarction, non–ST-segment–elevated acute coronary syndromes, any myocardial revascularization procedure, heart failure needing at least hospitalization, fatal and nonfatal strokes, any aortic or lower limb revascularization procedure and renal events, defined as a chronic kidney disease stage 3 or higher (estimated glomerular filtration rate <60 mL/min per 1.73 m^2).

Calculations

PP was calculated as systolic BP (SBP)–diastolic BP (DBP). MBP was calculated as 1/3 PP+DBP. The SBP white-coat effect (sWCE) was calculated as the difference between office SBP and average 24-h SBP at ambulatory BP measurement and the heart rate white-coat effect as the difference between office heart rate and average 24-hour heart rate. For the analysis, participants were divided into PP tertiles (first tertile [T1; n=432]: range, 20.0–46.7 mm Hg; second tertile [T2; n=405]: range, 46.7–55.7 mm Hg; third tertile [T3; n=404]: 55.8–95.7 mm Hg) and MBP tertiles.

Statistical Analysis

Data are presented as mean±SD unless specified. Differences between means were assessed by 1-way ANCOVA adjusting for age and sex, unless specified. The associations between PP and other clinical variables were investigated with Pearson correlation test, and the occurrence of spuriously significant results was excluded by Bonferroni adjustment. The independent predictors of PP were estimated with multivariate least-square regression analysis, adjusting for several clinical variables. The risk of development of hypertension requiring pharmacological treatment related to PP and MBP tertile was evaluated by means of multivariable Cox analyses, adjusting for risk factors and confounders. Subsequently, a final model was developed in which PP and MBP tertiles were entered as the first variables and then adjusted for all the other variables that were found to be significant (final parsimonious model).[19] The same analysis was repeated for the risk of major adverse cardiovascular events (MACE). A 2-tailed $P<0.05$ was considered significant. All analyses were performed using Systat version 11 and 12 (SPAA Inc, Evanston, IL) and Medcalc version 15.8 (MedCalc Software, Ostend, Belgium).

Results

Men were younger than women (32.2±8.5 versus 35.7±7.6 years; $P<0.001$) and had higher office SBP (146.1±10.2 versus 144.1±10.8 mm Hg; $P=0.003$) and PP (52.4±11.4 versus 49.4±9.4; $P=0.003$). Mean BP was similar in the 2 sexes ($P=0.84$). As shown in the Figure, among men, PP was highest in the youngest age group (60.7 mm Hg) and then it gradually decreased and reached the lowest values in the 2 oldest groups. Among women, PP decreased from the first to the second age group (from 51.7 to 45.4 mm Hg) and then it gradually increased and reached the highest value in the oldest age group. Of note, PP in women was lower than in men until 37 years of age, but after that age, it was higher in women. ISH was present in 14.5% of men and 4.3% of women. In 11.6% of people with ISH, MBP was above the median in the whole cohort (111.1 mm Hg).

The baseline characteristics of the study participants by office PP tertiles are reported in Table 1. Patients in the highest PP tertile were younger, were more frequently men, had higher heart rate, drank less alcohol, and were more frequently active in sports compared with those in the 2 lower tertiles. As expected, patients in the highest PP tertile had higher SBP and lower DBP, either in the office or at ambulatory measurement. The sWCE was significantly higher in the top PP tertile than in the 2 lower ones as was the heart rate white-coat effect. There was no significant difference for metabolic data, except for triglycerides, which were lower in the highest PP tertile. SV and cardiac index (n=827) were significantly higher among patients in the highest PP tertile than among those in the other tertiles.

Table 1. Baseline Characteristics of 1241 Study Participants According to Pulse Pressure Tertiles

Variable	First Tertile (n=432)	Second Tertile (n=405)	Third Tertile (n=404)	*P* Value
Age, y	34.1±7.4	34.2±8.1	31.0±9.5	<0.001*
Sex (M), %	69.7	72.6	78.5	0.014†
Height, m	1.73±0.09	1.73±0.91	1.74±0.95	0.25
BMI, kg/m^2	25.5±3.4	25.6±3.5	25.5±3.4	0.93
Smokers, %	19.9	23.0	18.6	0.28†
Alcohol drinkers, %	53.7	49.4	42.6	0.005†
Coffee drinkers, %	73.8	75.8	74.0	0.77†
Active in sports, %	30.6	37.5	45.6	<0.001†
SBP, mm Hg	136.6±7.3	145.5±5.1	155.6±8.1	<0.001
DBP, mm Hg	95.9±5.8	94.4±4.6	91.5±7.2	<0.001
HR, bpm	72.3±8.5	74.8±9.3	76.5±10.2	<0.001
24-h SBP, mm Hg	127.9±9.8	130.5±10.6	134.5±11.1	<0.001
24-h DBP, mm Hg	82.6±7.1	82.0±7.9	79.8±9.0	0.006
24-h HR, mm Hg	74.1±7.1	73.4±8.2	71.4±8.7	<0.001
sWCE, mm Hg	8.7±12.2	14.8±11.2	21.0±12.5	<0.001
HRWCE, bpm	–1.82±8.1	1.34±9.4	5.12±9.6	<0.001
Serum glucose, mmol/L	5.18±0.17	5.16±0.72	5.20±0.68	0.13
Total cholesterol, mmol/L	5.15±0.99	5.19±0.96	5.03±0.99	0.83
HDL-cholesterol, mmol/L	1.34±0.35	1.36±0.36	1.34±0.30	0.24
Triglycerides, mmol/L	3.24±1.24	2.97±1.83	2.79±2.14	0.001‡
Stroke volume, mL	76.6±16.1	78.5±16.8	82.2±16.5	0.001
Cardiac index, mL/min per meter square	3.0±0.6	3.0±0.7	3.3±0.7	<0.001

Data are mean±SD and are adjusted for age and sex. BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; HRWCE, heart rate white-coat effect; SBP, systolic blood pressure; and sWCE, systolic white-coat effect.

*Adjusted for sex.

†Data unadjusted.

‡*P* value for log-transformed data.

Cross-Sectional Determinants of PP

At univariate analysis, office PP was correlated with MBP (r=0.23), heart rate (r=0.21), and the sWCE (r=0.45), all P<0.001. The correlation with the sWCE remained significant in both sexes separately (data not shown). In multivariate least-square regression analysis, significant determinants of office PP were male sex, younger age, lower body mass index, physical activity, smoking, sWCE, heart rate white-coat effect, and SV (Table 2). Independent correlates of 24-hour ambulatory PP were male sex, younger age, physical activity, alcohol intake, smoking, sWCE (inverse relationship), heart rate white-coat effect, serum glucose, and SV. In all regressions, the variance inflation factor was <2.0 for all variables.

Follow-Up

During 12.1 years (interquartile range, 5.1–17.4 years), 65.1% of the study participants developed hypertension requiring pharmacological treatment. In multivariate Cox analysis adjusted for age and sex, participants in the top PP tertile had a lower risk of developing hypertension needing treatment than those in the bottom tertile (Table 3). Inclusion in the model of body mass index, parental history of hypertension, parental history of cardiovascular disease, coffee and alcohol intake, physical activity habits, smoking, heart rate, serum glucose, and total cholesterol (model 1) did not attenuate the strength of this relationship (Table 3). However, when also the sWCE was included

Table 2. Significant Determinants of Office Pulse Pressure in 1241 Study Participants

Variable	Coefficient	SE	*P* Value
Age, y	–0.211	0.037	<0.001
Sex (men)	1.812	0.691	0.009
Smoking	0.855	0.300	0.004
Physical activity	1.416	0.277	<0.001
sWCE	0.363	0.021	<0.001
HRWCE	0.226	0.038	<0.001
Stroke volume*	0.104	0.020	<0.001
Body mass index	–0.178	0.081	0.029

Summary of multiple linear regression analysis. Data are also adjusted for heart rate, coffee and alcohol intake, total cholesterol, and serum glucose. HRWCE indicates heart rate white-coat effect; and sWCE, systolic white-coat effect.

*n=827.

Table 3. HRs (95% CI) for Risk of Hypertension

	Pulse Pressure Tertile		Mean Blood Pressure Tertile	
Cox Model	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age and sex adjusted	2nd 0.89 (0.75–1.06)	0.19	2nd 1.53 (1.28–1.84)	<0.0001
	3rd 0.76 (0.62–0.91)	0.004	3rd 1.90 (1.57- 2.30)	<0.0001
Model 1*	2nd 0.88 (0.74–1.05)	0.15	2nd 1.53 (1.27–1.85)	<0.0001
	3rd 0.75 (0.62–0.91)	0.003	3rd 1.91 (1.57–2.33)	<0.0001
Model 1 + sWCE (Model 2)	2nd 0.93 (0.78–1.11)	0.46	2nd 1.58 (1.31–1.91)	<0.0001
	3rd 0.84 (0.69–1.03)	0.09	3rd 2.04 (1.66–2.50)	<0.0001
Model 2 + SV (Model 3)†	2nd 1.02 (0.82–1.27)	0.82	2nd 1.56 (1.25–1.96)	0.0001
	3rd 0.83 (0.64–1.07)	0.14	3rd 1.96 (1.53–2.51)	<0.0001

Results of Cox regression analyses in 1241 study participants. The first tertile was considered as the reference group. CI indicates confidence interval; HR, hazard ratio; sWCE, systolic white-coat effect; and SV, stroke volume.

*Model 1 included age, sex, parental history of hypertension, parental history of cardiovascular disease, coffee and alcohol intake, physical activity habits, smoking, resting heart rate, body mass index, serum glucose, and total cholesterol.

†n=827.

in the model the association of office PP with future hypertension ceased to be statistically significant. Office MBP was a strong independent predictor of future hypertension in all models (Table 3). Office DBP showed a weaker association with future hypertension than MBP did (data not shown). When we included ambulatory BP instead of office BP data in the multivariable regressions, 24-hour PP did not show any relationship with this outcome. Using the bottom tertile as a reference, the hazard ratio was 0.89 (95% confidence interval [CI], 0.75–1.05) for the second, and 0.83 (0.69–1.01) for the top 24-hour PP tertile. In contrast, the association remained significant for 24-hour MBP with a hazard ratio of 1.45 (95% CI, 1.21–1.73) for the second tertile and of 2.03 (1.70–2.42) for the top tertile.

During the follow-up, there were 62 fatal and nonfatal MACE (5.5% among the men and 3.6% among the women). The most common MACE were coronary events (n=32). Coronary events included 1 fatal and 19 nonfatal cases of acute myocardial infarction, 9 acute coronary syndromes, and 3 coronary revascularizations. The incidence of fatal (n=1) and nonfatal stroke amounted to 11 cases. Other MACE included 3 cases of heart failure requiring hospitalization, 3 cases of aortic aneurism, 6 cases of peripheral vascular disease, and 7 cases with renal events. In multivariable Cox analysis (see model 1 in Table 3), people in the highest office PP tertile had a lower risk of MACE than those in the bottom tertile with a hazard ratio of 0.35 (95% CI, 0.17–0.73; *P*=0.005). However, inclusion of the sWCE in the regression attenuated the association with office PP to borderline statistical significance (*P*=0.045). In contrast, office MBP was an independent predictor of MACE in the multivariable model (hazard ratio, 3.06; 95% CI, 1.32–7.09; *P*=0.009), an association that was not weakened by inclusion of the sWCE in the regression (*P*=0.003). Office DBP was not associated with MACE. When ambulatory PP was included in the models instead of office PP, 24-hour PP did not show any relationship with MACE in any model (data not shown). When coronary events were considered as the outcome variable, the hazard ratio from the multivariable model (model 1) was 0.30, 95% CI, 0.09 to 0.93, *P*=0.038, for the top versus the bottom office PP tertile and was 7.29, 95% CI, 1.41 to 37.66, *P*=0.018, for the top office MBP tertile.

Discussion

The present data show that in young subjects screened for stage 1 hypertension, office PP is a negative predictor of future hypertension needing treatment and of MACE and that only MBP is associated with increased risk of adverse outcome. The associations with MACE were driven primarily by differences in risk of coronary events. The negative relationship with future hypertension was no longer present when the sWCE was included in the survival models and was of borderline statistical significance for MACE. When 24-hour ambulatory PP was used instead of office PP, no association was found for both outcomes.

Office PP is a well-known predictor of cardiovascular events and mortality in elderly people.[1–4] This association was shown either in general populations[2] or in hypertensive samples.[3,20] Much less is known about the clinical significance of PP in young individuals for the obvious reason that a long follow-up is needed to collect a sufficient number of events. Sesso et al[9] in a large general population of male individuals confirmed that PP was an important predictor of cardiovascular disease in people aged ≥60 years.[9] However, among people

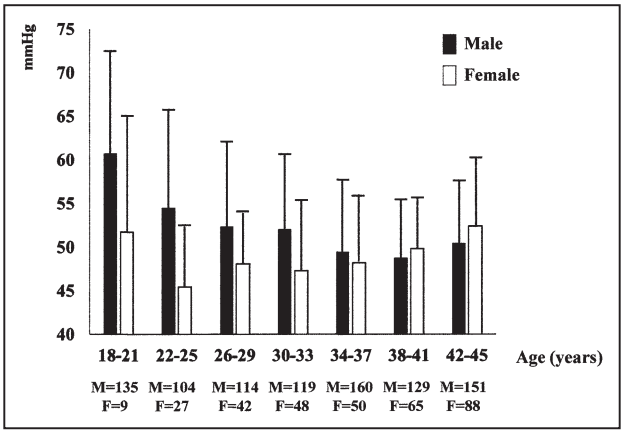

Figure. Pulse pressure in 1241 HARVEST (Hypertension Ambulatory Recording Venetia Study) participants grouped according to age and gender. The bars represent mean±SD. M indicates males; and F, females.

aged <60 years (mean, 48.5 years), PP provided a negligible prognostic information. More recently, the risk of cardiovascular disease in young- to middle-aged individuals (mean age, 34 years) was studied by Yano et al[10] in people stratified by sex and hypertension subtype.[10] These authors found that compared with men with optimal-normal BP, men with ISH had a 23% increase in risk of cardiovascular disease mortality, a risk similar to that in men with high-normal BP. At variance, among the women with ISH, the risk of cardiovascular disease mortality was higher than in those with high-normal BP or isolated diastolic hypertension. However, in that study, the prognostic capacity of PP and MBP separately was not investigated.

Pathogenetic Considerations

Whether elevated PP in youth should be considered an ominous or innocent sign has been debated for long. So-called spurious systolic hypertension was first described by O'Rourke et al.[21] and Mahmud and Freely[22] in small groups of apparently healthy young men who were often participants in sports activities. These individuals with elevated PP were considered to have exaggerated amplification of the arterial pressure wave traveling to the periphery. In a later study, Hulsen et al[8] observed this condition in 16.2% of a large population of young men who exhibited a high brachial SBP but a normal aortic systolic pressure measured with a noninvasive technique. According to the above authors, elevated PP in these individuals was because of high arterial distensibility and was to be considered a benign condition.

In the Tecumseh study, Julius et al[23] observed that young participants with high SBP were characterized by a hyperkinetic state with increased cardiac index and high plasma norepinephrine levels, suggesting sympathetic overactivity. In the more recent Enigma study performed in a larger number of individuals aged 17 to 27 years, McEniery et al[7] confirmed that a significant contributor to high PP was increased SV. However, in that study, also increased arterial stiffness estimated from pulse wave velocity was an independent determinant of PP though its contribution to PP was smaller than that provided by SV (2% versus 6% change in R^2). In the Enigma study, MBP showed a much stronger association with pulse wave velocity than did PP.

In keeping with the above data, in the present study, SV was an independent correlate of office PP, suggesting the existence of a hyperkinetic state in our participants with elevated PP. The significant relationship of SV also with 24-hour PP indicates that the hyperkinetic state may not be present only at the time of the medical assessment but may be an actual contributor to increased PP during the 24 hours. In addition, in agreement with previous studies,[22] participation in sports was another variable associated with increased PP. However, the strongest determinant of PP was the sWCE whose association with PP remained virtually unchanged when SV was included in the model. After incorporation of the sWCE in the survival analysis, the negative association between PP and hypertension or MACE tended to disappear. This suggests that the main determinant of elevated office PP in these individuals is a strong alarm reaction to the medical visit. This finding is in keeping with previous results by Julius et al[23] in young people with hyperkinetic hypertension[23] and by Lurbe et al[24] in children. In the latter study, children with ISH and normal central SBP were characterized by an elevated sWCE.[24]

Elevated PP and ISH in youth are typical for the male sex as documented by several previous reports.[8,21,22,25] In the present study, we confirmed that high PP was more prevalent among the men than among the women especially in the younger age categories.

Limitations

We acknowledge that the present study has several limitations. First, a possible limitation is the relatively small number of MACE. However, in the parsimonious Cox models, only 6 to 7 variables remained included and a generally accepted statistical principle is that there should be ≈10 events for every variable fitted in a multivariable Cox model.[19] Another limitation is that MBP was calculated as DBP plus one third of the difference between SBP and DBP measured with the traditional auscultatory method, which assumes that the pressure wave shape is the same in all persons. Only actual waveform measurement with either an invasive[26] or a noninvasive[27] technique would allow an accurate analysis of the sphygmic wave and, therefore, a precise quantification of MBP that may vary in different individuals according to the shape of the pressure wave. Heart rate is another potential modifier of MBP,[28,29] and in an effort to minimize our methodological inaccuracy, we also included resting heart rate in the regression models. In addition, we enrolled only whites and could not estimate meaningful differences between men and women because of the lower number of participants and MACE among the women. Therefore, the present results may not be applicable to women or to people of other racial backgrounds. Another limitation is the lack of data on arterial elasticity and central BP, which would have allowed us to better characterize the hemodynamic profile of our participants. One strength of the present study is the quality of the data source. Participants were checked periodically throughout the study keeping them under careful observation, and BP was also measured with 24-hour ambulatory monitoring.

Perspectives

Our data show that young- to middle-aged subjects with high PP measured either in the office or with ambulatory monitoring are at low risk of developing sustained hypertension or MACE. Office PP values that would be considered ominous in the elderly have no detrimental effect in young- to middle-aged subjects in whom they are mainly the result of a strong white-coat reaction to the medical environment. These findings mainly apply to the male sex. This does not necessarily mean that all young men with ISH are at low cardiovascular risk. In the present study, 11.6% of subjects with ISH had an MBP above the median of the whole group, which may imply an increase in risk. The present results suggest that young people with elevated PP and normal MBP should be followed with nonpharmacological measures and that antihypertensive drug treatment may be deferred.

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Disclosures

None.

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Novelty and Significance

What Is New?

- The predictive capacity of pulse pressure for development of future hypertension and major adverse cardiovascular events was tested for the first time in a cohort of young subjects screened for stage 1 hypertension.

What Is Relevant?

- In patients aged <45 years of age, an elevated pulse pressure measured either in the office or with ambulatory monitoring is not a predictor of adverse outcome. Only mean blood pressure has a predictive capacity for unfavorable outcome.

Summary

In young- to middle-aged subjects screened for stage 1 hypertension, high office pulse pressure was a negative predictor of future hypertension and major adverse cardiovascular events. This finding mainly applies to male individuals. Young people with elevated pulse pressure and normal mean blood pressure should be followed with nonpharmacological measures and antihypertensive drug treatment may be deferred.

Office Pulse Pressure Is a Predictor of Favorable Outcome in Young- to Middle-Aged Subjects With Stage 1 Hypertension

Francesca Saladini, Claudio Fania, Lucio Mos, Adriano Mazzer, Edoardo Casiglia and Paolo Palatini

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ONLINE SUPPLEMENT

Office pulse pressure is a predictor of favourable outcome in young to middle age subjects with stage 1 hypertension

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Supplemental material: 3 paragraphs, 3 tables.

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METHODS

Procedures

Smokers were classified into 4 categories according to the daily number of cigarettes smoked: non smokers, 1-5 cigarettes/day, 6-10 cigarettes/day, and >10 cigarettes/day. Alcohol intake was calculated by summing the total number of milliliters of daily alcohol consumption of wine, beer and liqueurs according to the formula of Criqui et al (15). Participants were then divided into three categories of alcohol use: 0 g/day, <50 g/day, ≥50g/day. Coffee consumption was categorized according to the number of caffeine-containing cups of coffee drunk per day: nondrinkers (0 cups/day) and drinkers (1 or more cups/day). Physical activity was assessed using a standardized questionnaire. Activities were classified on the basis of relative intensity, adapting the activity intensity codes established and validated by the Minnesota Heart Survey (1). For the present analysis subjects were categorized as sedentary if they did not regularly perform any physical activity and physically active if they performed leisure physical activities or sports activities. A family history of cardiovascular disease was defined as myocardial infarction, stroke, or sudden death before the age of 60 in a first-degree relative. Secondary forms of hypertension were excluded on the basis of a complete history and physical examination and by routine diagnostic procedures. These included serum potassium, urinalysis, plasma renin activity, plasma and urinary aldosterone and urinary catecholamines. To further exclude the presence of renovascular disease, all patients underwent a Doppler examination of the renal arteries or renal scintigraphy. All subjects underwent physical examination and anthropometry. After an overnight fast, a morning sample of blood was obtained to measure routine blood chemistry including serum glucose and lipid profile.

Definition of operational threshold level

The operational threshold level for identifying participants who needed antihypertensive treatment changed over time in keeping with available guidelines. In 1990, when we started the study, the British Hypertension Society stipulated that eligibility for antihypertensive medication was progression to grade II hypertension (supine office systolic blood pressure ≥160 mm Hg and/or supine office diastolic blood pressure ≥100 mm Hg) during the first year of follow-up (2,3). Later on the 1999 ISH/WHO guidelines for patients at low cardiovascular risk such as the participants in the present study, established that treatment should be given to subjects with a supine office systolic blood pressure ≥150 mm Hg and/or supine office diastolic blood pressure ≥95 mm Hg in two consecutive visits (4). After the publication of the 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension (5), which adopted the 140/90 mmHg cut-off also for subjects at low risk, we finally used the 140/90 mmHg threshold.

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