Conventional Antihypertensive Drug Therapy Does Not Prevent the Increase of Pulse Pressure With Age

Jean-Jacques Mourad, Jacques Blacher, Patrick Blin, Ursula Warzocha, on behalf of the investigators of the PHASTE study*

Abstract—Increased pulse pressure (PP), an independent predictor of cardiovascular risk, may be quantified on the basis of the prevalence of isolated systolic hypertension (ISH) in the population at large. The purpose of this study was to estimate the prevalence of ISH and its relation to age and drug therapy in a large group of outpatient hypertensive subjects in France. Between March and December 1999, 2975 French general practitioners included 17 716 consecutive patients with uncontrolled hypertension (systolic blood pressure \( SBP \) \( \geq 140 \) mm Hg and/or diastolic blood pressure \( DBP \) \( > 90 \) mm Hg), either treated or not treated. They were asked to complete a questionnaire concerning associated cardiovascular risk factors and ongoing antihypertensive therapy. Subjects were classified according to 5 age ranges (from 18 to 103 years). In each age range, SBP, DBP, mean blood pressure, and PP were significantly lower \((P<0.001)\) in treated subjects than in untreated subjects, with the exception of PP in subjects \( \geq 75 \) years. The latter finding resulted from a significant increase of SBP and PP with age, together with a significant lowering of DBP with age, irrespective of drug treatment. Subsequently, the prevalence of ISH increased with age from 20.4\% to 35.2\% in men and women. In any given age range, drug therapy for hypertension is associated with marginally lower values of PP. In the studied populations, the increase of PP with age is independent of gender and of the presence of antihypertensive drug treatment, leading to an increased prevalence of ISH and a subsequent increase of cardiovascular risk with age. \( \text{Hypertension. 2001;38:958-962.} \) 

Key Words: hypertension, essential \( \square \) antihypertensive therapy \( \square \) blood pressure \( \square \) pulse

In the early therapeutic trials of hypertension,\(^1\) diastolic blood pressure (DBP) was the unique criterion of inclusion. Thus, historically, subjects with isolated systolic hypertension (ISH) have been excluded from groups of hypertensive subjects treated by drug therapy.\(^2\) ISH was considered to be a benign state related to the physiological age increase of arterial stiffness, with a resulting increase of systolic blood pressure (SBP) and decrease of DBP. More recently, this conventional interpretation has been reviewed on the basis of 3 main findings. First, the Systolic Hypertension in the Elderly Program (SHEP)\(^3\) has shown that in older subjects with ISH, drug treatment for hypertension markedly reduced cardiovascular morbidity and mortality, even to a larger extent than in populations of subjects with systolic-diastolic hypertension. Second, increased pulse pressure (PP), which is the main characteristic feature of ISH patients, is a significant predictor of cardiovascular risk, independent of (and in addition to) SBP, DBP, and mean blood pressure (MBP).\(^4\text{-}8\)

Finally, in subjects treated for hypertension, particularly those with systolic-diastolic hypertension, DBP is frequently controlled \((\leq 90 \) mm Hg\)), whereas SBP remains elevated \((\geq 140 \) mm Hg\)), resulting in an increased prevalence of ISH.\(^9\text{-}12\) Such observations raise 2 important questions. First, what is the real prevalence of ISH in populations at large, whether treated or untreated for hypertension? Second, what is the relative contribution of aging and drug treatment in the decrease of DBP observed in hypertensive subjects age \( \geq 50 \) years treated in the long term?

In the present study, a large population of hypertensive subjects either treated or untreated has been screened in France. Treated and untreated hypertensive subjects have been analyzed and compared at different age ranges.

Methods

From March to December 1999, 17 716 consecutive hypertensive patients were selected by 2975 French general practitioners as having sustained high blood pressure either treated or untreated. In all subjects, high blood pressure was defined as a SBP \( > 140 \) mm Hg and/or a DBP \( > 90 \) mm Hg, measured by mercury sphygmomanometry with subjects in the supine position, with a minimum of 3 casual measurements during the last month.
Information compiled from the questionnaire filled out at inclusion included gender, age, family (first-degree relatives), history of premature cardiovascular events (for men, age <55 years; for women, age <60 years), personal history of diabetes mellitus and/or dyslipidemia, smoking habits, previous diseases, and use of medications, including antihypertensive drugs.

The blood pressure and biological measurements were performed in subjects in the morning after an overnight fast, with each subject in the supine position. Brachial blood pressure was measured with a mercury sphygmomanometer after 15 minutes of rest. Phases I and V of the Korotkoff sounds were considered SBP and DBP, respectively. MBP was calculated as DBP\(+\) (SBP\(-\)DBP)/3. Three measurements 2 minutes apart were averaged. PP was the difference between SBP and DBP.

Statistical Analysis
For the statistical evaluation, subjects were classified into 5 age ranges. Values are presented as mean±1 SD. Treated versus untreated subjects and men versus women were compared by using \(t\) tests for each age range, and the effect of age was tested within treated and untreated groups by use of 2-way ANOVA, with gender as an adjusting effect. A value of \(P=0.05\) was considered to be significant.

Results
Patients with isolated systolic hypertension (n=4589, 25.9%) were those with SBP >140 mm Hg and DBP <90 mm Hg. The cohort was composed of 17 716 hypertensive subjects (53.5% men and 46.5% women) aged 62±12 (mean±1 SD) years. Of the 17 716 patients, 72.4% were treated with antihypertensive drug therapy; the mean number of antihypertensive drugs was 1.4 per patient. The antihypertensive drugs included various classes: calcium antagonists (20.0%), diuretics (25.0%), \(\beta\)-blocking agents (21.0%), ACE inhibitors (25.7%), central-acting agents (6.4%), angiotensin II antagonists (9.3%), and \(\alpha\)-blocking drugs (3.3%), either alone or in combination. Of the 17 716 patients, 2569 (14.5%) were medically treated for dyslipidemia (drugs including statins or fibrates), and 3153 (17.8%) were medically treated for diabetes mellitus (drugs including sulfamides, biguanidines, or insulin). Clinical characteristics of the population are indicated in Table 1.

Table 2 shows, for each age range, the mean value of SBP, DBP, MBP, and PP in the untreated and the treated populations. In each age range, SBP, DBP, and MBP were significantly lower \((P<0.001)\) in the treated population than in the untreated population. PP was marginally reduced only in treated subjects >75 years. In the overall population, SBP, DBP, and PP (but not MBP) increased with age \((P<0.001)\), whether the patients were under drug treatment or not. In none of these statistical evaluations was there an effect of drug class in treated subjects (data not shown).

### Table 1. Clinical Characteristics of the Studied Population

<table>
<thead>
<tr>
<th>Age</th>
<th>NT</th>
<th>T</th>
<th>Female subjects, %</th>
<th>NT</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>668</td>
<td>1383</td>
<td>1392</td>
<td>1088</td>
<td>348</td>
</tr>
<tr>
<td></td>
<td>698</td>
<td>2245</td>
<td>3457</td>
<td>4378</td>
<td>2059</td>
</tr>
<tr>
<td>NT</td>
<td>37.6</td>
<td>37.6</td>
<td>43.0</td>
<td>53.1</td>
<td>61.8</td>
</tr>
<tr>
<td>T</td>
<td>37.2</td>
<td>38.8</td>
<td>42.7</td>
<td>50.3</td>
<td>63.9</td>
</tr>
</tbody>
</table>

NT indicates untreated; T, treated.

### Table 2. Blood Pressure Measurements in the Studied Population

<table>
<thead>
<tr>
<th>Age</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
<th>MBP, mm Hg</th>
<th>PP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;45 y</td>
<td>45–54 y</td>
<td>55–64 y</td>
<td>65–74 y</td>
</tr>
<tr>
<td>NT</td>
<td>163±13</td>
<td>164±12</td>
<td>165±12</td>
<td>166±13</td>
</tr>
<tr>
<td>T</td>
<td>159±13*</td>
<td>160±12*</td>
<td>161±12*</td>
<td>162±12*</td>
</tr>
<tr>
<td>NT</td>
<td>96±9</td>
<td>96±9</td>
<td>95±9</td>
<td>94±9</td>
</tr>
<tr>
<td>T</td>
<td>94±9†</td>
<td>94±9*</td>
<td>93±9*</td>
<td>92±9*</td>
</tr>
<tr>
<td>NT</td>
<td>118±9</td>
<td>119±8</td>
<td>118±8</td>
<td>118±9</td>
</tr>
<tr>
<td>T</td>
<td>116±9*</td>
<td>116±8*</td>
<td>115±8*</td>
<td>115±9*</td>
</tr>
<tr>
<td>NT</td>
<td>67±12</td>
<td>68±12</td>
<td>70±12</td>
<td>72±12</td>
</tr>
<tr>
<td>T</td>
<td>65±12*</td>
<td>66±11*</td>
<td>68±11*</td>
<td>70±11*</td>
</tr>
</tbody>
</table>

Values are mean±1 SD. *(\(P<0.001\))* and †\((\(P<0.05\)) for NT vs T.‡Adjusted for gender.
The Figure shows that the prevalence of ISH increases markedly ($P < 0.001$) with age, from 20.4% to 35.2%, with a significantly higher prevalence in treated hypertensive patients ($P < 0.001$).

**Discussion**

In the present study, we determined the following in a large population of hypertensive patients: (1) for all ages, SBP, DBP, and MBP were significantly lower in treated subjects than in untreated subjects; (2) PP did not differ for individuals age $>75$ years in treated and untreated subjects. This finding was the consequence of a significant increase of SBP and decrease of DBP with age in the overall population, resulting in an increased prevalence of ISH with age, irrespective of the presence or absence of antihypertensive drug treatment.

The Figure shows that the prevalence of ISH increases markedly ($P < 0.001$) with age, from 20.4% to 35.2%, with a significantly higher prevalence in treated hypertensive patients ($P < 0.001$).

This investigation was cross-sectional by nature and, therefore, could not describe time-dependent relationships between age and blood pressure during a given follow-up. However, in the population of hypertensive subjects under chronic drug treatment, the observed difference in DBP was close to 4 mm Hg. Accordingly, this difference did not differ substantially from that observed under the earlier therapeutic trials, causing a significant decrease in cardiovascular morbidity and mortality.\(^1\) We did not find any clinically relevant decrease of PP in treated hypertensive subjects. This finding could not be considered as a simple surrogate indicating an increase of SBP with age. Indeed in subjects age $>65$ years, the observed increase in SBP was associated with a concomitant decrease of DBP. This result was not a consequence of chronic drug treatment because the same finding was observed in the treated and untreated hypertensive populations. Thus, the weight of evidence suggests that the altered PP and, subsequently, the increased prevalence of ISH with age raises the issue of a change in the relationship between high blood pressure and cardiovascular aging in hypertensive subjects.

In untreated hypertensive subjects, ISH is a very classic hemodynamic pattern, particularly in subjects age $>65$ years and mainly in women. The results of the SHEP study\(^3\) have shown that in this population, chronic antihypertensive drug treatment prevents the occurrence of stroke, congestive heart failure, and coronary heart disease to the same or greater extent as in the younger hypertensive population. The present study indicates that currently the population of subjects with ISH should include younger subjects (age, 40 to 65 years), particularly males, and that the prevalence of ISH in this population increases substantially in subjects aged between 45 and 80 years. This population of patients, which had never been included in therapeutic trials involving hypertensive subjects in middle age, is not really an emerging population. First, the hemodynamic pattern of ISH has been reported for many years in large epidemiological and clinical studies and is attributed to cardiac factors in younger subjects and to increased aortic stiffness in older subjects.\(^13\) Second, many epidemiological investigations have conclusively shown that SBP increases markedly with age, whereas DBP becomes stable or, in some cases, falls for those age $>50$ years, favoring the presence of ISH.\(^14,15\) More specifically, the proportion of untreated hypertensive subjects whose DBP is increased $>100$ mm Hg and tends to fall further with time is $\approx 16\%$, according to the studies of Bulpitt et al.\(^16\) Finally, in a recent long-term longitudinal study, we have identified that in populations at large, the higher degree of cardiovascular risk was observed predominantly in subjects who develop higher SBP and, simultaneously, falling DBP with age but not in subjects who develop a combined increase of SBP and DBP.\(^17\)

An important finding of the present study was that ISH increased with age not only in untreated but even more in treated hypertensive subjects. Numerous studies have recently shown that on the one hand, DBP is often well controlled by chronic antihypertensive drug treatment ($\leq 90$ mm Hg), and on the other hand, the prevalence of controlled SBP ($\leq 140$ mm Hg) is substantially less, resulting in an increased prevalence of ISH in subjects treated by...
antihypertensive drug therapy. Several therapeutic trials have recently confirmed the following result. First, in the elderly, drug treatment lowers SBP and DBP in subjects with systolic-diastolic hypertension. This means that DBP is better controlled than SBP, resulting in an elevated proportion of subjects with ISH. In younger populations, as observed in the Hypertension Optimal Treatment (HOT) study, a similar finding is shown. Despite an active drug therapy, which is able to significantly decrease DBP to <90 mm Hg, the decrease of SBP does not occur to a similar extent, resulting in the persistence of an elevated PP. It is interesting to note that the substantial decrease of DBP, which is obtained in the HOT study, is not associated with a subsequent decrease of cardiovascular risk. This latter finding is important to consider inasmuch as PP associated with a subsequent decrease of cardiovascular risk. The latter is the main hemodynamic mechanism for increased SBP and PP in the aging population. The latter is the main hemodynamic mechanism for increased SBP and PP in the aging population.

In conclusion, the present study has shown that in a French population of hypertensive subjects, an elevated prevalence of patients with ISH is now developing independently of the presence or absence of drug treatment. This population probably results from the increase of longevity in populations at large and from the interactions between the presence of hypertension and of the coexisting age-induced increase in arterial stiffness. The latter is the main hemodynamic mechanism for increased SBP and PP in the aging population. Whether a specific treatment for this alteration should be important to consider at the present time was not determined in the present study and requires further investigation.

Acknowledgments

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References

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