Sexual Dimorphism in the Transition From Masked to Sustained Hypertension in Healthy Youths

Empar Lurbe, Lutgarde Thijs, Maria Isabel Torro, Julio Alvarez, Jan A. Staessen, Josep Redon

Abstract—The risk and factors related to the development of hypertension among healthy youths with elevated ambulatory and normal conventional blood pressure, masked hypertension, have not been established. We performed a long-term follow-up study assessing how hypertension develops over time in healthy, masked hypertensive youths. The potential sex dimorphism in the incidence and timing of the development of hypertension has been analyzed. In a long-term follow-up study (median follow-up, 36 months), we enrolled 272 healthy conventional normotensive youths (aged 6–18 years; 55.8% girls) of whom 39 had masked hypertension at baseline. Development of sustained hypertension (hypertension in both conventional and ambulatory measurement) was recorded. The daytime systolic blood pressure increased from baseline to last available follow-up in boys (3.5 mmHg; \(P<0.001\)) but not in girls (0.7 mmHg; \(P=0.23\)), leading to a significant between-sex difference (\(P=0.0022\)). The incidence of sustained hypertension was 7.0/100 subjects/y (n=12) in masked hypertensives and 0.6/100 subjects/y (n=4) in normotensives. Masked hypertensive boys more frequently proceeded to sustained hypertension as compared with masked hypertensive girls (50.0% versus 17.4%; \(P=0.041\)). Masked hypertension at baseline (hazard ratio, 15.6; 95% confidence interval, 4.91–49.7; \(P<0.0001\)) and male sex (hazard ratio, 3.25; 95% confidence interval, 1.12–9.39; \(P=0.0295\)) were independent factors associated with the incidence of sustained hypertension during the follow-up. In youth, masked hypertension is a precursor of sustained hypertension. The risk of developing sustained hypertension is higher in boys than it is for girls. The fact that masked hypertension is not prognostically innocent increases the importance of the diagnosis at an early age. (Hypertension, 2013;62:00-00.)

Key Words: ambulatory blood pressure monitoring ■ child ■ hypertension ■ masked hypertension ■ sex dimorphism

Clinicians who care for children and adolescents are now facing changes in hypertension, which include new methods for measuring blood pressure (BP) and assessing associated cardiovascular risk factors and target organ damage. Although conventional BP should be used as a reference method for measuring BP and diagnosing hypertension, ambulatory BP monitoring (ABPM) has been introduced into the pediatric population. According to European and American recommendations, ABPM is now increasingly recognized as being a valuable tool in the diagnosis and management of hypertension in children and adolescents.\(^1\)-\(^3\) Longitudinal studies with repeated measurements have shown that ABPM is prognostically useful for some pathological conditions.\(^4\)-\(^5\) The potential role of ABPM in the identification of children who are at greatest risk to develop hypertension, for whom targeted prevention programs are expected to be most beneficial, has not been assessed.

Masked hypertension, elevated ambulatory BP in the presence of normal conventional BP, is a condition that, in adults, has been associated with organ damage\(^6\) and cardiovascular risk, similar to that for sustained hypertension (both conventional and ambulatory hypertension).\(^7\)-\(^9\) In childhood, masked hypertension has received little attention, despite a prevalence of \(\approx\)10%; it persists in 40% of the subjects and has been associated with left ventricular hypertrophy.\(^10\)-\(^13\)

If an elevation in ambulatory BP precedes the development of sustained hypertension, further knowledge of the risk factors associated with this BP increase can be valuable in the management of hypertension in children and adolescents. To address this issue, we performed a long-term follow-up study assessing how sustained hypertension develops over time in healthy, masked hypertensive youths. The potential sex dimorphism in the incidence and timing of the development of hypertension has been analyzed.

Methods

This is an extension of a previous follow-up report\(^12\) starting in November 1990 with a total of 10617 person-months. We enrolled...
youths aged 6 to 18 years, who attended the pediatric outpatient clinic of the General Hospital of the University of Valencia for a preventive health check-up. We excluded concomitant disease by physical examination, blood biochemistry, and analysis of a urine sample. The study included 272 subjects, with normal conventional BP at baseline. In all subjects, ambulatory BP was recorded at baseline and at least once during follow-up with a total number of 736 recordings. The Institutional Committee for the Protection of Human Subjects approved the study. All parents and participants ≥ 12 years gave informed, written consent.

A standardized questionnaire to obtain information on the parental history of hypertension was completed for all participants. Body weight was recorded ≥ 0.1 kg with the subjects wearing light indoor clothing and no shoes. Height was recorded to the nearest 0.5 cm using a standardized wall-mounted height board. Obesity was diagnosed when body mass index (BMI, the weight in kilograms divided by the square of the height in meters) exceeded the 95th percentile for age and sex. The extent of obesity was quantified on the basis of BMI z score using Cole Least Mean Square method. 14 The ambulatory recordings were initiated on regular school days between 08:30 and 09:00 AM. On monitoring days, the participants did not engage in vigorous exercise. The oscillometric SpaceLabs 90207 and 90217 monitors (SpaceLabs Inc, Redmond, WA) were programmed to obtain BP readings at 20-minute intervals from 06:00 hours until midnight and at 30-minute intervals from midnight until 06:00 hours. Daytime was defined as the interval ranging from 10:00 to 20:00 hours and nighttime from midnight to 06:00 hours. Measurements were automatically repeated when readings were outside the ranges of 70 to 220 mm Hg systolic or 40 to 140 mm Hg diastolic. We did not otherwise edit the ambulatory recordings. Only recordings with ≥80% of successful measurements, defined as the percentage of valid preset measurements, were included.

On monitoring days, BP was measured on the nondominant arm, with cuff and bladder size adjusted to upper-arm girth. The 3 measurements of each office visit were averaged for analysis. For ABPM, cuff and bladder size were adjusted as for office BP. The averages of the valid readings for the 24-hour daytime and nighttime, respectively, were calculated. Within individual subjects the means of the ambulatory BP were weighted by the time interval between consecutive readings. 13

Using the published diagnostic thresholds, hypertension in children and adolescents was defined as office BP persistently ≥ 95th percentile, specific for age, sex, and height. Children with average systolic BP or diastolic BP ≥ 90th percentile but < 95th percentile were classified as having high-normal BP. Adolescents with BP≥120/80 mm Hg, even if < 90th percentile, were also considered as having high-normal BP. Ambulatory hypertension was defined as awake BP persistently ≥ 95th percentile, specific for sex and age or height. 13 Cross-classifying the conventional and ambulatory BPs, 4 subgroups were delineated: 1) sustained normotensives, 2) sustained hypertensives, 3) white-coat hypertensives, and 4) masked hypertensives. Sustained normotension was defined as normotensive for both conventional and ambulatory measurements. Similarly, sustained hypertension was hypertensive for both conventional and ambulatory measurements. Similarly, sustained hypertension was hypertensive for both conventional and ambulatory measurements. Similarly, sustained hypertension was hypertensive for both conventional and ambulatory measurements. Similarly, sustained hypertension was hypertensive for both conventional and ambulatory measurements. Similarly, sustained hypertension was hypertensive for both conventional and ambulatory measurements. Similarly, sustained hypertension was hypertensive for both conventional and ambulatory measurements. Similarly, sustained hypertension was hypertensive for both conventional and ambulatory measurements. Similarly, sustained hypertension was hypertensive for both conventional and ambulatory measurements. Similarly, sustained hypertension was hypertensive for both conventional and ambulatory measurements.

Results

Baseline Characteristics

A total of 272 young white subjects were included in the study, of which 152 (55.8%) were girls. Parental history of reported hypertension was similar in girls and boys (P=0.14), whereas obesity was more prevalent in boys (P=0.03). Mean age (P=0.46), BMI (P=0.73), and the conventional and ambulatory BPs (P=0.27) were similar for both sexes. The prevalence of masked hypertension was similar (P=0.73) in boys (n=16, 13.3%) and in girls (n=23, 15.1%).

Baseline characteristics according to the presence or the absence of masked hypertension at baseline are shown in the Table. Normotensive children and those with masked hypertension had similar age, body mass, and prevalence of obesity. Boys, but not girls, with masked hypertension more frequently reported a parental history of hypertension than their normotensive counterparts (50.0% versus 23.1%; P<0.05). Compared with normotensive subjects, participants with masked hypertension had significantly higher conventional and ambulatory BPs.

Sex and Changes in BP Throughout Follow-Up

Median follow-up (36 months; 5th–95th percentile interval, 7–92 months) was similar (P=0.55) in boys and girls. The increase in the conventional systolic BP from baseline to last available follow-up was greater (P=0.015) in boys (3.3 mm Hg/y; 95% confidence interval [CI], 2.2–4.3; P<0.0001) than in girls (1.2 mm Hg/y; 95% CI, −0.1 to 2.4; P=0.062). Similarly, the daytime systolic BP increased from baseline to last available follow-up in boys (3.5 mm Hg; 95% CI, 2.2–4.8; P<0.0001) but not in girls (0.7 mm Hg; 95% CI, −0.5 to 2.0; P=0.23), leading to a significant between-sex difference (P=0.0022).

During the follow-up, 13 girls (56.5%) and 6 boys (37.5%) masked at baseline became normotensive. Likewise, 6 girls (26.1%) and 1 boy (6.2%) maintained masked hypertension category. Girls with masked hypertension at baseline were more likely to progress to sustained hypertension during follow-up as compared with girls with normotensive daytime BPs at baseline (n=4 [17.4%] versus n=1 [0.8%; P=0.0019]). Similarly, more (P<0.001) boys with masked hypertension at baseline developed sustained hypertension as compared with boys who were normotensive at baseline (n=8 [50.0%] versus n=2 [1.9%; P<0.0001]). Moreover, masked hypertensive boys more frequently proceeded to sustained hypertension as compared with masked hypertensive girls (50.0% versus 17.4%; P=0.041).

Masked Hypertension and the Risk of Developing Sustained Hypertension

Median follow-up was longer (P=0.016) in the masked hypertensives (45 months; percentile interval, 5–135) as compared with the normotensives (35 months; percentile interval, 7–80 months). Taking into account all follow-up visits, the incidence of sustained hypertension was 7.0 per 100 subjects/y (n=12) in masked hypertensives and 0.6/100 subjects/y (n=4) in normotensives. Masked hypertension at baseline (hazard ratio, 15.6; 95% CI, 4.91–49.7; P<0.0001)
and male sex (hazard ratio, 3.25; 95% CI, 1.12–9.39; $P = 0.0295$) were independent factors associated with the incidence of sustained hypertension during the follow-up. The results were confirmed when other variables were included in the model (conventional systolic BP at baseline, family history of hypertension, BMI $z$-score at baseline, change in BMI $z$-score from baseline to follow-up and baseline daytime pulse rate). The incidence of sustained hypertension over time according to the presence or the absence of masked hypertension at baseline is shown in the Figure. In a sensitive analysis, considering only 4 years of follow-up, to adjust for the longer follow-up in masked hypertensives as compared with normotensives, 13 subjects developed sustained hypertension. In this sensitivity analysis, masked hypertension was still significantly associated with the incidence of sustained hypertension (hazard ratio, 20.8; CI, 5.7–75.6; $P < 0.001$).

**Discussion**

The present study, the first to analyze the long-term prognostic value of masked hypertension to progress to hypertension in youths, has established that masked hypertension is a precursor of sustained hypertension. Moreover, the risk of developing sustained hypertension is higher in masked hypertensive boys when compared with masked hypertensive girls.

Fifty percent of masked boys at baseline progressed to sustained hypertension. For girls, in contrast, 1 in 4 remained masked, and few of them developed sustained hypertension. Indeed, the yearly rate of systolic BP increment was 3.2 and 1.1 mmHg in boys and 1.2 and −0.2 mmHg in girls, for office and daytime ambulatory BP, respectively. These findings show a sexual dimorphism for BP, in which growth pattern and gonadal hormones may play a role. The persistence of the masked phenomenon in girls means the risk of progressing in the short to medium term persists. Because it is well known that BP tracks from childhood into adulthood, the low rate of progression to sustained hypertension is in agreement with the lower incidence and prevalence of hypertension in girls as compared with that for boys in young adulthood. Whether the persistence of masked hypertension in girls is a risk condition for developing hypertension during pregnancy or from the use of hormonal contraceptive pills should be further explored, especially in this age group, one that frequently does not receive continuous medical attention.

The present clinical research has focused on the potential value of 24-hour ABPM in clinical normotensive subjects. This should remain distinct from the aim of clarifying the clinical place of 24-hour ABPM in subjects with a diagnosis of hypertension.

### Table. Baseline Characteristics According to the Presence or the Absence of Masked Hypertension at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Girls (n=152)</th>
<th>Boys (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sustained NT (n=129)</td>
<td>Masked HTN (n=23)</td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>24 (18.6)</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Obesity</td>
<td>10 (7.8)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Mean values±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>9.7±2.6</td>
<td>9.3±2.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>19.7±3.7</td>
<td>20.2±3.0</td>
</tr>
<tr>
<td>Conventional BP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>97.1±8.0</td>
<td>103.3±9.9†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>56.0±7.6</td>
<td>56.4±7.2</td>
</tr>
<tr>
<td>Ambulatory BP, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-h systolic</td>
<td>107.3±7.5</td>
<td>122.9±5.0‡</td>
</tr>
<tr>
<td>Daytime systolic</td>
<td>111.5±8.1</td>
<td>127.9±4.8‡</td>
</tr>
<tr>
<td>Nighttime systolic</td>
<td>100.3±8.1</td>
<td>114.2±7.9†</td>
</tr>
<tr>
<td>24-h diastolic</td>
<td>63.7±4.8</td>
<td>71.7±4.3‡</td>
</tr>
<tr>
<td>Daytime diastolic</td>
<td>68.5±5.2</td>
<td>77.4±4.3‡</td>
</tr>
<tr>
<td>Nighttime diastolic</td>
<td>55.2±6.1</td>
<td>62.0±6.6‡</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; HTN, hypertension; and NT, normotension.

* $P<0.05$, † $P<0.01$, and ‡ $P<0.001$, for the comparison between masked HTN and NT. Obesity defined as body mass index ≥95th percentile for age and sex.14
of hypertension or with underlying disease prone to elevated BP, such as type 1 diabetes mellitus or chronic kidney disease.1 This is relevant from a diagnostic point of view, underlining the complementary value of ABPM to conventional BP measurement taken in a clinical setting (office BP) in a pediatric population. Using ABPM, masked hypertension has been identified as a relatively frequent, noninnocent condition, between 10.9% and 14% in adults.18–20 It has been associated not only with target organ damage,21 increased risk of sustained hypertension, and high cardiovascular morbidity and mortality2,3,19,22–24 but also with an increase in risk of developing new onset diabetes mellitus.25 In children and adolescents, few published studies have explored this condition.11–15 The persistence of the phenomenon in ≈40% of the subjects12 has been confirmed with a longer follow-up in the present study. Furthermore, the increased risk of developing hypertension in these subjects indicates that masked hypertension in childhood should be regarded as a condition that requires further follow-up and intervention in those in whom the disorder persists.

The fact that masked hypertension is not prognostically innocent and that it carries an increased risk of cardiovascular morbidity,3,9 increases the importance of diagnosis at an early age. Therefore, ABPM should be performed in subjects at risk of having masked hypertension. A parental history of hypertension has been reported more frequently in masked hypertensive youths and is the most relevant differential clinical characteristic.

The apparent discrepancy between the impact of family history of hypertension on the prevalence of masked hypertension and on the risk of progressing to hypertension merits additional comment. Population-based epidemiological studies have described the familial aggregation of hypertension.26,27 Offspring from hypertensive parents have both a higher prevalence and incidence of hypertension, as well as higher BP values when these are compared with those from the offspring of normotensive parents.28,29 Indeed, family history of hypertension seems to be a clinical characteristic that should be taken into account when deciding whether to perform an ABPM in otherwise normotensive children. In clinical practice, the number of potential candidates for ABPM is limited because the prevalence of hypertension is relatively low in parents of such a young age.30

The study has to be interpreted within the context of its limitations. The hypothesis found its origin in clinical practice. Clinical indications and the time required to enroll the children explain why the number of follow-up visits and the interval between visits varied from 1 subject to another. However, sensitivity analyses taking into account only the first 4 years of follow-up were confirmatory. The diagnosis of office and ambulatory hypertension is, of course, inextricably tied to the operational BP threshold. The normative data for the interpretation of conventional and ambulatory BP readings in children and adolescents are those recommended by the Scientific Statements of the American Heart Association and the European Society of Hypertension.13 Potential strengths of the study include its prospective nature with a large number of follow-up recordings. The results were obtained from a group of children and adolescents initially diagnosed as masked hypertensives as compared with a group of normotensives with similar age and sex distribution, in which the incidence of office hypertension was similar to the incidence (0.3% per year), reported recently in an epidemiological study which included repeated conventional BP measurements.31

Perspectives

The findings of the present study have important implications for the diagnosis and treatment of hypertension in children and adolescents and for future research. From a diagnostic point of view, our observations underline the complementary use of ambulatory BP monitoring with conventional BP measurement in a clinical setting and establish masked hypertension as a precursor of sustained hypertension, especially in boys. Indeed, 24-hour ABPM should be performed in youths with a parental history of hypertension at a relatively young age to detect the masked condition early and, subsequently, recommend actions to halt further BP increments. The presence of the masked condition warrants follow-up, especially in this age group, one that frequently does not receive continuous medical attention. Once the persistence of masked hypertension is established, left ventricular mass should be assessed, and if left ventricular hypertrophy is detected, BP-lowering therapy should be started in youth.

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Disclosures

None.

References

What Is New?

- The first study to analyze the long-term prognostic value of masked hypertension to progress to hypertension in youths. The risk of developing sustained hypertension is higher in masked hypertensive boys when compared with masked hypertensive girls.

What Is Relevant?

- From a diagnostic point of view, it reinforces the evidence of the complementary value of ambulatory blood pressure monitoring to conventional blood pressure measurement in a pediatric population.

Novelty and Significance

- Masked hypertension in childhood should be regarded as a condition that requires further follow-up and intervention in those in whom the disorder persists.

Summary

Masked hypertension is a precursor of sustained hypertension, especially in boys. The fact that masked hypertension is not prognostically innocent increases the importance of the diagnosis at an early age. The presence of the masked condition warrants follow-up.
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