

Prevalence and Clinical Significance of Isolated Ambulatory Hypertension in Young Subjects Screened for Stage 1 Hypertension

Paolo Palatini, Mikolaj Winnicki, Massimo Santonastaso, Lucio Mos, Daniele Longo, Vania Zaetta, Marta Dal Follo, Tiziano Biasion, Achille C. Pessina

Abstract—Little is known about the clinical significance of isolated ambulatory hypertension, a condition characterized by low office but elevated ambulatory blood pressure. This study aimed to investigate the prevalence and the predictive value of isolated ambulatory hypertension diagnosed after 3 months of observation for the development of sustained hypertension within a cohort of 871 never-treated stage-1 hypertensive subjects. The study end point was progression to more severe hypertension and need of antihypertensive medication. In 244 subjects (28%), clinic blood pressure declined to <140/90 mm Hg after 3 months. Of these, 124 (14.2% of total) had low clinic and ambulatory blood pressures after 3 months (nonhypertensive subjects), whereas 120 subjects (13.8% of total) showed low clinic but elevated ambulatory blood pressure (isolated ambulatory hypertension). During the 6 years of observation, the number of end points based on multiple clinic blood pressure readings progressively increased from the nonhypertensive subjects (19%) to the subjects with isolated ambulatory hypertension (35%) and to the subjects with high clinic and high ambulatory blood pressures (65%, $P<0.0001$). In an adjusted proportional hazard model, isolated ambulatory hypertension status was associated with a 2.2 ($P=0.02$) increase in the risk of reaching the end point in comparison with the nonhypertensive subjects. Final ambulatory systolic blood pressure was also higher in the former than the latter ($P=0.03$). Our results indicate that among subjects screened for stage 1 hypertension, individuals with isolated ambulatory hypertension after 3 months of observation have increased risk of developing sustained hypertension in later life compared with subjects in whom both clinic and ambulatory blood pressures are normal. (*Hypertension*. 2004; 44:170-174.)

Key Words: blood pressure monitoring, ambulatory ■ hypertension, detection and control

A large body of evidence suggests that ambulatory blood pressure (ABP) monitoring is superior to clinic blood pressure (CBP) measurement for the management of the hypertensive patient.¹⁻³ ABP monitoring is a fundamental tool in identifying patients with white-coat hypertension and in evaluating treatment efficacy after antihypertensive therapy has been initiated.¹⁻⁴ Recently, ABP monitoring has been approved for reimbursement in the United States for patients with suspected white-coat hypertension. It is useful to determine the appropriate management of white-coat hypertension because subjects with this condition are at low risk, so that antihypertensive treatment could be deferred.⁵ Much less is known about the opposite condition, isolated ambulatory hypertension (IAH), which is often referred to as masked hypertension.^{6,7} This definition applies to patients in whom CBP is low but ABP is elevated, a condition that remains hidden until ABP monitoring is performed. Two recent reports showed that IAH diagnosed either with ABP moni-

toring⁸ or self blood pressure measurement⁹ was a significant predictor of cardiovascular morbidity in elderly patients. The problem for clinical practice is how to identify these patients because ABP monitoring will never be performed in subjects who appear to be normotensive at CBP assessment. According to a recent document of the European Society of Hypertension, the phenomenon should be suspected in individuals who have had an increased CBP at some time, which would justify ABP monitoring assessment in these subjects.¹⁰ However, the prevalence of IAH in subjects with transiently elevated blood pressure and its clinical significance in youth or adulthood is still unknown.

The aim of the present study was to investigate the prevalence of IAH and its predictive value for the development of sustained hypertension in a group of young subjects with transiently elevated CBP values. This issue was explored in the frame of the Hypertension and Ambulatory Recording Venetia Study (HARVEST), a multicenter longitudinal

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From the Clinica Medica 4 (P.P., M.W., D.L., V.Z., A.C.P.), University of Padova; Town Hospital (M.S.), Vittorio Veneto; Town Hospital (L.M.), San Daniele del Friuli; Town Hospital (M.D.F.), Trento; and Town Hospital (T.B.), Rovereto-Ala, Italy.

Correspondence to Professor Paolo Palatini, MD, trial coordinator, Clinica Medica 4, University of Padova via Giustiniani, 2-35128 Padova, Italy. E-mail palatini@unipd.it

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study that enrolls subjects never treated for hypertension and who exhibit stage 1 hypertension at baseline examination.^{11,12}

Methods

Study Subjects

The present analysis was carried out in 871 white subjects taking part in the HARVEST study who had ABP monitoring data after 3 months of follow-up.^{11,12} None of the subjects had received any antihypertensive treatment before the study. The study was approved by the HARVEST Ethics Committee, and written informed consent was given by the participants. The procedures followed were in accordance with institutional guidelines. At the baseline (first 2 clinic visits within 2 weeks), all subjects underwent physical examination, anthropometry, blood and urine sampling, office blood pressure and 24-hour ABP measurements, ECG, echocardiography, and 24-hour urinary albumin measurement. The mean of 6 office readings taken in the supine position during the 2 visits was used to define baseline CBP.^{11,12} Subjects with baseline diastolic CBP between 90 and 99 mm Hg, systolic CBP between 140 and 159 mm Hg, or both were enrolled. The criteria and the procedures used for CBP and ABP measurement were reported elsewhere.^{11,12} We used 135/85 mm Hg as the threshold for normal mean daytime ABP.¹⁰ Body mass index (BMI) was used as an index of obesity (weight/height²). The data included a medical and family history and a questionnaire of current use of alcoholic beverages and tobacco and physical activity habits. All subjects were given medical advice on lifestyle modifications. Echocardiography was obtained in 671 subjects, in 609 of whom M-mode images were technically satisfactory by criteria published elsewhere.¹³ Left ventricular hypertrophy was defined as a left ventricular mass >125 g/m² in men and >110 g/m² in women.¹⁴ Microalbuminuria was defined as an albumin excretion rate \geq 30 mg/24 h.

Follow-Up

Follow-up data were reported for those participants who performed at least one 24-hour blood pressure recording after the 3-month evaluation. After baseline examination, follow-up visits were scheduled at 1, 2, and 3 months.¹⁵ Patients were then seen after 3 months and every 6 months thereafter. ABP monitoring was performed at the baseline, after 3 months, 5 years, 10 years, or just before starting antihypertensive treatment in the patients who reached the end point. The last available ABP monitoring was used to calculate final ABP. The end point was the development of sustained hypertension and the need for antihypertensive medication in accordance with international guidelines.¹⁵

Data Analysis

Subjects were divided into subgroups according to their CBP and ABP after 3 months of observation (Figure 1). Nonhypertensive (NonH) subjects had CBP <140/90 mm Hg and mean daytime ABP <135/85 mm Hg; IAH subjects had CBP <140/90 mm Hg but elevated ABP (daytime systolic blood pressure \geq 135 mm Hg or daytime diastolic blood pressure \geq 85 mm Hg). Hypertensive (HT) subjects had an elevation of both CBP and ABP. In the present analysis we excluded 209 subjects with an elevated CBP (systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg) but an ABP <135/85 mm Hg (subjects with white-coat hypertension), leaving 662 subjects as the study population. Differences between groups were assessed by 1-way ANCOVA adjusting for age, sex, BMI, and lifestyle factors. χ^2 analysis and Fisher exact test were used for the categorical variables. Cox proportional hazard regression was used to calculate hazard ratios of developing the end point and their 95% confidence intervals (CIs). In multivariate models, adjustments were made for age, sex, BMI, and lifestyle factors. Data are presented as mean \pm SEM, unless specified. A $P < 0.05$ was considered statistically significant. The SAS program was used for statistical analysis (SAS, Inc).

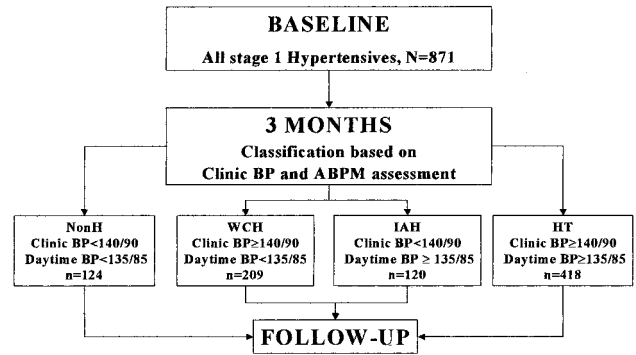


Figure 1. Subject classification. ABPM indicates ambulatory blood pressure monitoring; NonH, nonhypertensive subjects (includes normotensive and prehypertensive subjects according to JNC 7); WCH, white-coat hypertensive subjects; IAH, isolated ambulatory hypertensive subjects; HT, sustained hypertensive subjects.

Results

In 244 subjects (28%), both systolic and diastolic CBPs declined to <140/90 mm Hg after 3 months, whereas in the other 627 (72%), CBP was still in the hypertensive range. Of the 244 subjects with CBP <140/90 mm Hg, 124 (14.2% of total) were identified as NonH according to both CBP and ABP after 3 months, whereas 120 subjects (13.8% of total) showed a CBP <140/90 mm Hg but elevated ABP and were defined as IAH subjects. Among the NonH subjects, 4 had normal CBP according to the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7; <120/80 mm Hg), whereas 120 had CBP in the prehypertensive range. Among the IAH subjects, the respective figures were 5 and 115. Among the 627 subjects with high CBP, 418 (48% of total) also had high ABP and were thus defined as HT. Clinical characteristics for these 3 groups are presented in Table 1. HT subjects were slightly older and heavier than NonH subjects or IAH individuals. No differences in sex distribution or lifestyle factors were found between the groups. As expected, CBP and ABP were higher in the HT than the NonH subjects (Table 2). CBP was slightly but insignificantly higher in the IAH than the NonH subjects, and ABP was higher in the HT than the IAH group. On standing, diastolic CBP increased in all subjects without significant differences between the 3 groups, and systolic CBP showed a tendency to decline, which was smaller in the IAH subjects than the other 2 groups. The percentages of smokers, alcohol drinkers, and sedentary subjects at the baseline assessment (enrollment) were similar in the 3 groups. After 3 months, 9.8% of NonH, 8.6% of IAH, and 6.3% of HT improved their lifestyle (differences nonsignificant). A decrease in body weight from baseline to 3-month assessment was observed in all subjects (-2.5 ± 1.4 kg in NonH, -2.5 ± 1.4 kg in IAH, and -3.8 ± 0.8 kg in HT) without significant differences between the 3 groups. In a multiple linear regression, which included age, sex, BMI, lifestyle factors, and CBP, the only significant predictor of IAH was the difference between standing and lying systolic blood pressure ($P = 0.02$).

Left ventricular hypertrophy and microalbuminuria tended to increase in the HT and IAH subjects as compared with the

TABLE 1. Baseline Characteristics of the Study Groups

Variable	NonH (n=124)	IAH (n=120)	HT (n=418)	P
Age, years	32±0.8	34±0.8	34±0.4*	0.048
Body mass index, kg/m ²	24.7±0.3	25.0±0.3	26.0±0.2†‡	<0.001
Females, n (%)	38 (31%)	36 (30%)	103 (25%)	NS
Smokers, n (%)	18 (15%)	28 (23%)	95 (23%)	NS
Alcohol drinkers, n (%)	51 (41%)	55 (47%)	208 (50%)	NS
Coffee drinkers, n (%)	87 (70%)	78 (65%)	321 (77%)	NS
Physically active, n (%)	44 (35%)	48 (40%)	155 (37%)	NS
Microalbuminuria, %	2.6	6.9	8.8	NS
Left ventricular hypertrophy, %	4.4	7.1	6.7	NS

Values are means±SEM.

P is related to ANOVA trend for continuous variables and to χ^2 for categorical variables.

*P<0.05 vs NonH; †P<0.001 vs NonH; ‡P=0.02 vs IAH.

NonH individuals (Table 1). However, the differences were not statistically significant for left ventricular hypertrophy and were of borderline significance ($P=0.08$) for microalbuminuria.

Follow-Up

During follow-up, 242 of the 492 patients who had final ABP, and were thus considered for this analysis, reached the target end point and were given antihypertensive therapy, whereas the other 250 remained untreated. Mean follow-up duration was 62±2 months in the end point subjects and was 82±1 months in the non-end point subjects. The rate of subjects reaching the end point was much higher in the HT subjects than the other 2 groups and was higher in the subjects with IAH than the NonH individuals (Figure 2). Compared with the NonH individuals, the adjusted relative risk of developing sustained hypertension was 2.25 times higher (95% CI, 1.33 to 3.86, $P=0.019$) in the subjects with IAH and 6.52 times higher (95% CI, 4.64 to 10.27, $P<0.0001$) in the HT subjects. Final ABP was higher in the HT and IAH individuals than in the group of NonH subjects (Figure 3). Both CBP and ABP were elevated at final assessment ($P<0.0001$) in 76% of HT subjects, 47% of IAH individuals, and 31% of NonH subjects.

In a multiple linear regression in which final ABP was the dependent variable, IAH and HT, adjusted for baseline data, were both significant independent predictors of final systolic ABP ($P<0.001$) and final diastolic ABP ($P<0.001$).

Discussion

According to JNC 7 guidelines, subjects with stage 1 hypertension and mild to moderate cardiovascular risk should be followed for at least 2 months before deciding whether they need antihypertensive treatment.⁵ If after this time CBP declines to <140/90 mm Hg, no antihypertensive medication should be given unless compelling indications are present. In this study, among the subjects whose CBP had normalized within the first 3 months of observation, ABP monitoring identified a subgroup of patients with high ABP, a condition known as IAH. In the IAH patients, there was a trend for a more frequent involvement of target organs at the time of enrollment in comparison with the NonH subjects, a rate which was similar to that in the HT patients. However, the between-group differences were not statistically significant because of the low prevalence of cardiac and renal abnormalities in our population. The prospective study showed that IAH subjects were more likely to develop sustained hyper-

TABLE 2. Clinic and Ambulatory Blood Pressures of the Study Groups After 3 Months of Observation

Variable	NonH (n=124)	IAH (n=120)	HT (n=418)	P ANOVA
Supine clinic SBP, mm Hg	128.8±0.8	130.4±0.9	146.6±0.5‡§	<0.001
Supine clinic DBP, mm Hg	82.2±0.6	84.1±0.6	94.6±0.3‡§	<0.001
Standing-supine SBP Δ , mm Hg	-3.3±0.7	-0.6±0.8*	-2.8±0.4†	0.026
Standing-supine DBP Δ , mm Hg	3.8±0.5	4.4±0.6	4.7±0.3	NS
Daytime SBP, mm Hg	123.7±0.8	137.4±0.8‡	140.1±0.4‡†	<0.001
Daytime DBP, mm Hg	77±0.7	83.9±0.7‡	87.3±0.4‡§	<0.001
Nighttime SBP, mm Hg	108.8±1.0	119.1±1.0‡	122.6±0.6‡†	<0.001
Nighttime DBP, mm Hg	67.6±0.7	72.0±0.7‡	76.2±0.4‡§	<0.001

Values are means±SEM.

Δ indicates difference (a positive value denotes a higher blood pressure in the standing than the supine posture).

*P<0.05 vs NonH, †P<0.05 vs IAH, ‡P<0.001 vs NonH, §P<0.001 vs IAH.

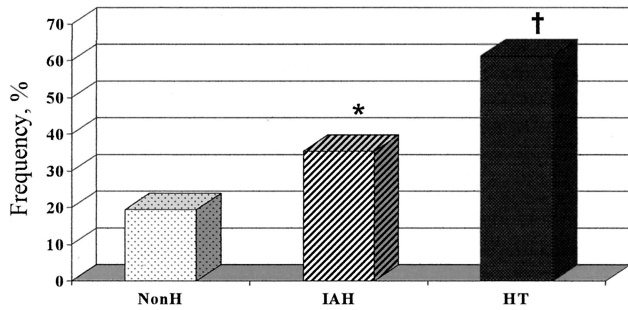


Figure 2. Frequency of subjects reaching the end point during the follow-up. * $P=0.019$ vs NonH; † $P<0.001$ vs others.

tension in later life than the NonH subjects irrespective of whether hypertension was defined on the basis of CBP, ABP, or both. Subjects who had high CBP and high ABP after 3 months had the highest rate of sustained hypertension at follow-up.

The present knowledge on the clinical significance of IAH is still limited. Some investigators reported more extensive target organ damage in IAH subjects compared with normotensive individuals,^{8,16–18} in keeping with the present results. The prognostic significance of IAH in prospective studies has been evaluated only in 2 cohorts of elderly subjects. In a population of 578 untreated 70-year-old men assessed with ABP monitoring, Bjorklund et al found a higher rate of cardiovascular events during follow-up in a group of IAH patients than a group of nonH subjects.⁸ Recently, among 4939 treated 70-year-old hypertensive subjects, Bobrie et al observed that the subjects with elevated blood pressure at home, but not in the office, had a higher incidence of cardiovascular events during a 3.2-year follow-up than the subjects with controlled hypertension in both settings.⁹ The prevalence and the clinical significance of IAH might differ in the elderly compared with younger subjects. ABP shows much less increase with age than CBP, and an ABP higher than CBP can be found less frequently in old individuals than in young subjects.¹⁹ In a report by Rasmussen et al,²⁰ 82% of 42-year-old men had higher daytime blood pressure than office blood pressure, whereas this was true of only 51% of men aged 72 years. This suggests that IAH is more common in the young than the elderly, and the pathogenetic mechanisms of IAH might differ at different ages. The present results were obtained in a sample of 18- to 45-year-old subjects with a mean age of 33 years. Obviously, the rate of

cardiovascular events is very low in this age range and, thus, we had to rely on a soft end point, the development of sustained hypertension. However, the diagnosis of hypertension was made during a prolonged period of observation and was based not only on multiple CBP readings but also on ABP monitoring.

The reason why subjects with low CBP may have elevated ABP is still unknown. Factors that could selectively raise ABP might be smoking,^{21,22} alcohol drinking,²³ sedentary habits,¹¹ or greater reactivity to daily life stressors.²⁴ In the present study, only the difference between standing and lying systolic blood pressure was a significant predictor of IAH. Blood pressure reaction to standing is more pronounced in young individuals and is known to affect average daytime blood pressure.^{25–27} In previous studies, we found that the blood pressure response to standing was inversely correlated to the difference between CBP and daytime blood pressure.^{25,26} Subjects with increased reaction to standing exhibited higher systolic and diastolic ABP levels despite a similar supine systolic CBP and lower supine diastolic CBP compared with the subjects with normal reaction.²⁶ Recently, Raikonen et al observed that the difference between daytime and nighttime blood pressures is greater in subjects with pronounced cardiovascular responses to changes in posture.²⁷ Overall, these data indicate that increased reactivity to standing is predictive of higher ABP and of increased daytime blood pressure in particular. This may explain why subjects with increased reactivity to standing are more likely to have IAH. We do not have information on patterns of physical activity during the recordings and, thus, we cannot exclude that our IAH subjects were more physically active than the NonH subjects during the day. However, the higher ABP observed in the IAH individuals, also at repeat recording, argues against this possibility.

Perspectives

If it is accepted that ABP is a better predictor of outcome than CBP, it is logical to assume that in many subjects diagnosis of true hypertension is missed by CBP assessment. But how subjects with IAH can be identified remains virtually unknown because this condition can hardly be predicted by a subject's clinical characteristics.²⁸ Our results indicate that this condition should be sought in those subjects who are referred for stage 1 hypertension and are found normotensive or prehypertensive on repeat CBP testing. In fact, 50% of these subjects actually exhibit high blood pressure in the ambulatory setting and a large proportion of them develop sustained hypertension over 6 years, despite recommendations about lifestyle modifications. These findings suggest that subjects with transient CBP elevation and IAH may benefit from drug therapy.

Appendix

List of the Centers Participating in the HARVEST Study

Belluno-Cardiologia: G. Catania; Cremona-Div. Medica: G. Garavelli; Dolo-Div. Medica: F. Pegoraro, S. Laurini; Mirano-Cardiologia: D. D'Este; Padova-Clinica Medica 4: F. Dorigatti, D. Longo, V. Zaetta, P. Frezza; Pordenone-Centro Cardioreumato-

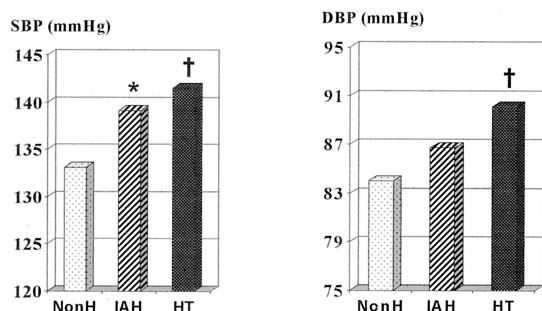


Figure 3. Final daytime ambulatory blood pressure of the study groups. * $P=0.027$ vs NonH; † $P<0.001$ vs NonH.

logico: G. Cignacco, G. Zanata; Portogruaro-Div. Medica: R. Gelsio; Rovereto-Ala-Div. Medica: M. Mattarei, T. Biasion; Rovigo-Cardiologia: P. Zoncin, A. Bortolazzi; San Daniele del Friuli-Area di Emergenza: L. Mos, S. Martina, O. Vrizz; San Donà di Piave-Cardiologia: L. Milani, C. Canali; Trento-Div. Medica: G. Devenuto, M. Dal Follo; Treviso-Div. Nefrologia: G. Calconi, P. Gatti; Vittorio Veneto-Div. Medica: M. Santonastaso, E. Cozzutti, R. Garbelotto, A. Mazzer. President: C. Dal Palù; Vice President: A.C. Pessina; Trial Coordinator: P. Palatini.

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