Alterations of Cardiac Structure in Patients With Isolated Office, Ambulatory, or Home Hypertension

Data From the General Population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study)

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Background—The prevalence and clinical significance of isolated office (or white coat) hypertension is controversial, and population data are limited. We studied the prevalence of this condition and its association with echocardiographic left ventricular mass in the general population of the PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) Study.

Methods and Results—The study involved a large, randomized sample (n=3200) representative of the Monza (Milan) population, 25 to 74 years of age. Participants in the study (64% of the sample) underwent measurements of office, home, 24-hour ambulatory blood pressure, and echocardiography. Isolated office hypertension was defined as systolic or diastolic values $\geq 140$ mm Hg or $\geq 90$ mm Hg, respectively. Home and ambulatory normotension were defined according to criteria previously established from the PAMELA Study, for example, $<132/83$ mm Hg (systolic/diastolic) for home and 125/79 mm Hg for 24-hour average blood pressure. Treated hypertensive subjects were excluded from analysis that was made on a total of 1637 subjects. Depending on normotension being established on systolic or diastolic blood pressure measured at home or over 24 hours, the prevalence of isolated office hypertension ranged from 9% to 12%. In these subjects, left ventricular mass index was greater ($P<0.01$) than in subjects with normotension both in and outside the office. This was the case also for prevalence of left ventricular hypertrophy. Left ventricular mass index and hypertrophy were similarly greater in subjects found to have normal office but elevated home or ambulatory blood pressure (affecting 10% of the population).

Conclusions—Isolated office hypertension has a noticeable prevalence in the population and is accompanied by structural cardiac alterations, suggesting that it is not an entirely harmless phenomenon. This is the case also for the opposite condition, that is, normal office but elevated home or ambulatory blood pressure, which implies that limiting blood pressure measurements to office values may not suffice in identification of subjects at risk.

Key Words: blood pressure • hypertension • hypertrophy

Despite years of extensive investigation, the clinical significance of isolated office hypertension,1 that is, the condition also termed “white coat hypertension”2 that is characterized by an elevated office but a normal home or ambulatory blood pressure (BP), remains uncertain.3 This is because longitudinal studies, aiming at determining the cardiovascular risk, besides having an uncontrolled nature, have reached different conclusions.4–11 Furthermore, different conclusions have been reached by cross-sectional studies aimed at determining whether or not isolated office hypertension is accompanied by metabolic abnormalities or organ damage.12–23 This may have originated from the higher or lower values used to define home or ambulatory BP normality.22 It also may have originated, however, from the different characteristics of the patients recruited or from a selection bias, that is, from the involvement of subjects because of their coming to the hypertension clinic.

The PAMELA Study (Pressioni Arteriose Monitorate E Loro Associazioni) was performed to determine the normality values of ambulatory and home BP in the population.23,24 Because the study protocol involved collection of echocardiographic data, we were able to examine whether an isolated elevation of office BP is accompanied by cardiac structural

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abnormalities, without two major limitations of cross-sectional studies: one, a relatively small sample size, and two, a bias in subject recruitment because of its limitation to patients examined in a hypertension clinic. We were additionally able to provide a large database on the opposite phenomenon, that is, the prevalence and cardiac structural abnormalities of that fraction of the population in which home or ambulatory BP is elevated whereas office BP is normal.25

**Methods**

**Population**

The PAMELA Study was performed cross-sectionally on 2051 men and women, from a sample of 3200 subjects 25 to 74 years of age, selected as being representative of the population of Monza (a town in the Northeast outskirts of Milan, Italy). The participation rate was ~64%, and the demographic characteristics and medical history (phone interview) of the nonparticipants were similar to those of the overall population.

The methods used in the PAMELA study have been previously described in detail.23,24 In brief, subjects were visited by a physician
in the morning of a working day (Monday to Friday) at an outpatient clinic in the S. Gerardo University Hospital of Monza. Three BP measurements (by mercury sphygmomanometer) were obtained in the sitting position, and the subject was then fitted with an ambulatory BP monitoring device (Spacelabs 90207) set to take oscillometric readings at 20-minute intervals for 24 hours. The subjects were asked to (1) carry out normal daily activities during the monitoring period and to return to the hospital the following day to disconnect the equipment and (2) to take self-measurements of BP at home, in the sitting position, and the subject was then fitted with an ambulatory systolic and diastolic BP values, which were first edited from artifacts according to preselected criteria. Subjects were divided into subgroups having (1) a normal office (<90 mm Hg) and 24-hour average diastolic BP (<79 mm Hg), (2) an elevated office (>90 mm Hg) but a normal 24-hour average diastolic BP, (3) a normal office but an elevated 24-hour average diastolic BP (≥79 mm Hg), and (4) an elevation of both office and 24-hour average diastolic BP. Similar subgroup subdivisions were done for systolic BP (normality value <140 mm Hg, <125 mm Hg, and <132 mm Hg, respectively, for office, 24-hour average, and home measurements). Upper limits of normality of 24-hour mean and home BP were derived from previous analysis of all PAMELA BP. Mean (±SD) BP and echocardiographic values were calculated for each subgroup after exclusion of subjects under antihypertensive treatment (n=403) to avoid the confounding effect of changes in left ventricular structure directly caused by antihypertensive drugs. The statistical significance of between-subgroup differences was tested by 2-way ANOVA. Multiple comparisons were done with Dunnett’s test and with the Student’s t test for unpaired groups. A value of P<0.05 was taken as the level of statistical significance.

### Results

#### Blood Pressure

As shown in Figure 1, in 67% of the subjects, office and ambulatory diastolic BP were both normal. In 12% of subjects, both BPs were elevated, whereas an elevation of only office diastolic BP (isolated office hypertension) was identified in 12% of the sample. The remaining 9% showed a normal office but an ambulatory diastolic BP that was higher than the upper normal 24-hour value (ambulatory hyperten-
Echocardiographic Values

Figure 3 shows that in the PAMELA population, left ventricular mass index and wall thickness (septal plus posterior wall thickness) had a substantially normal distribution, with values lower in women and progressively greater with aging. Compared with the group in which both office and 24-hour diastolic BP were normal, either value was significantly greater when only office or only ambulatory diastolic BP was elevated, a further increase being observed when the elevation involved both pressures (Table 1). Similar findings were obtained when normal or hypertensive subgroups were identified according to office versus ambulatory systolic BP (Table 1) and to office versus home systolic or diastolic BP (Table 2). Left ventricular hypertrophy was also more common in the subgroups with isolated office or ambulatory hypertension and most common in subgroups with both office and 24-hour or home BP elevations.

**Correlation of Echocardiographic Data for Sex and Age**

Tables 1 and 2 also show that in the 4 subgroups, there was some sex and age imbalance. However, for left ventricular mass index, findings similar to those previously described were obtained also when the analysis separately considered men and women (Figure 4) and when in each sex data were further adjusted for age (Figure 5). This was the case also for left ventricular wall thickness (data not shown). Compared with the group in which office and 24-hour diastolic BP were both normal, the left ventricular mass index was +8.7% greater ($P<0.01$) in the subgroup with isolated office diastolic BP elevation, +8.6% greater ($P<0.05$) in the subgroup with 24-hour diastolic BP elevation, and +14.7% greater in the subgroup with an elevation of both office and 24-hour diastolic BP. Similar increases were seen when subgroup classification was based on systolic and home BPs.

As shown in Table 1, in subjects with isolated office hypertension, 24-hour or home BP was slightly greater than in those of subjects in whom office and 24-hour or home BP were both normal. Furthermore, in subjects with ambulatory hypertension, office BP was slightly greater than that of subjects in whom office and 24-hour or home BP were both.

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**TABLE 2. Sex, Age, and Echocardiographic Values in Subgroups of Subjects With Normal or Elevated Office and/or Home Average Diastolic and Systolic Blood Pressure**

<table>
<thead>
<tr>
<th>Diastolic BP</th>
<th>Normal/Normal</th>
<th>Elevated/Normal</th>
<th>Normal/Elevated</th>
<th>Elevated/Elevated</th>
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<tr>
<td>n (%)</td>
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<td>M/F</td>
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<td>Age, y</td>
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<td>Mean office</td>
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<td>Mean 24-h</td>
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<td>LVMI, g/m²</td>
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<td>LWT, mm</td>
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<td>LVH, n (%)</td>
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<td>Data are shown as mean ± SD for each subgroup. LVMI indicates left ventricular mass index; LWT, left ventricular wall thickness; LVH, left ventricular hypertrophy. *P&lt;0.05; †P&lt;0.01 vs Elevated/Elevated.</td>
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normal. The left ventricular mass index values were thus further adjusted for (1) 24-hour BP in the isolated office hypertension subgroup and (2) office BP in the ambulatory hypertension subgroup. Compared with subjects in whom both pressures were normal, either the isolated office or the ambulatory hypertension subgroup continued to show greater left ventricular mass index values, with the differences remaining in most instances statistically significant (Figure 6). Similar findings were obtained for left ventricular wall thickness and for subgroup subdivision, based on home BP (data not shown).

Discussion

In our study, isolated office hypertension, that is, the condition characterized by a systolic or diastolic BP elevation in the clinic setting but with a normal BP in the ambulatory setting or at home, involved 9% to 12% of a population sample made up of untreated adult and elderly individuals, depending on whether the criterion to define daily life BP normality relied on ambulatory or home diastolic BP values or systolic BP values or both. Thus, the first finding of the present study is that in the population, isolated office hypertension has a noticeable prevalence. This prevalence, however, is less than that reported in several previous studies, which, however, (1) not infrequently had a limited sample size, (2) were mostly performed in hypertensive subjects and thus could not avoid a selection bias, and (3) used criteria to define daily life BP normality that were frequently not as stringent as those used in the present study (see below). It is therefore likely that the figures we found reflect more accurately than those of other studies how prevalent isolated office hypertension can really be in adults and elderly individuals. This applies to the characteristics of the population that we examined. That is a population with a maximum age of 74 years, which was taken from an urban environment and did not include treated hypertensive individuals to avoid direct effects of antihypertensive drugs on cardiac structure.

Another and perhaps more important finding of the present study is that in subjects with isolated office hypertension, left ventricular mass index and wall thickness were on average less than in subjects with both office and ambulatory or home daily life hypertension but greater than in subjects in whom BP was normal both in the office and in ambulatory conditions or at home, even when data were separately analyzed in men and women and adjusted for age. Furthermore, in these individuals, left ventricular hypertrophy was less common than in individuals with both office and daily life hypertension but clearly greater than in individuals with both office and daily life normotension. This suggests that isolated office hypertension may not be entirely harmless on clinical grounds. Namely, that whenever office BP is elevated, cardiac structure stands a greater chance of being altered as compared with subjects with office normotension. Because in
only relatively few instances this alteration did bring left ventricular mass index and wall thickness within hypertrophic values, this may not necessarily imply the need for immediate drug treatment. It indicates, however, that when isolated office hypertension is diagnosed, examinations aimed at assessing left ventricular structure (and possibly other markers of organ damage) are necessary and that if in the absence of cardiac or other organ damage, drug treatment is not implemented, a close follow-up of these patients in nevertheless advisable (possibly together with lifestyle changes that may reduce BP) because a greater tendency toward cardiac growth cannot be excluded. The conclusion that isolated office hypertension is not entirely devoid of an increased risk is not in line with a previous study7 whose observation, however, that isolated office hypertension is not accompanied by an increased incidence of cardiovascular morbidity events, lacked statistical power and was nevertheless accompanied, in some patients, by an increased left ventricular mass. It is, on the other hand, in line with the results of the Ohasama Study,31 in which cardiovascular death of patients characterized by office and home BP measurements was assessed over a long follow-up period.

A third new finding of our study deserves to be emphasized. Namely, that in ≈10% of the PAMELA population, (1) office BP normality was associated with ambulatory or home BP above normal values, and (2) in these individuals, average left ventricular mass index, average left ventricular wall thickness, and prevalence of left ventricular hypertrophy were similar to those seen in isolated office hypertensive subjects, that is, less than in subjects with both office and ambulatory or home hypertension but greater than in subjects with normal BP in and outside the physician’s office. A normal office BP may thus not infrequently coexist with an ambulatory or home BP elevation, although, because of the difference in upper normality values, office BP may remain higher than the out-of-office values. Under these circumstances, cardiac structure stands a greater chance to have an initial alteration or to be hypertrophic. This scores in favor of extending home and/or ambulatory BP measurements beyond the restricted use presently recommended by international guidelines on the diagnosis and treatment of hypertension1 to identify the fraction of the population in which office BP normality is accompanied by an elevation of daily-life BP and some alterations in cardiac structure. This fraction can only be discovered by home and ambulatory BP measurements, which can therefore more thoroughly identify the individuals in a population that may need a more close follow-up plus an earlier implementation of lifestyle changes that may reduce BP or oppose its elevation.

Several additional points must be discussed. First, the upper normality values of 24-hour and home BP used in our study are slightly lower than those reported by few other studies that have defined ambulatory and home BP through calculations different from those used for the PAMELA population.32 This does not weaken the interpretation of the present results, however. On the contrary, the more stringent definition of ambulatory and home BP normality used in the present study makes it more certain that no individuals with

![Figure 5. Left ventricular mass index (LVMI) in subjects after adjustment for age. Symbols as in Figure 4.](http://circ.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.101.139005)
some BP elevation outside the office were included, thereby strengthening the conclusion that isolated hypertension has clinical relevance. Second, only two thirds of the patients identified as having isolated office hypertension based on 24-hour BP normality also had isolated office hypertension based on home BP normality. Furthermore, in only approximately half of the patients with an elevation of 24-hour BP and a normal office BP, home BP, was concomitantly elevated. Thus, there is a limited agreement between ambulatory and home BP as far as their ability to diagnose a BP normality or elevation outside the physician’s office is concerned. This means that ambulatory and home BP both carry independent information made clinically relevant by their association with cardiac structure alterations. It also means that it is not possible to suggest that for diagnostic procedures one should proceed the other or vice versa.

Third, in patients with isolated office hypertension, 24-hour or home BP, despite being below the upper normality values, was on average somewhat greater than in patients in which both office and out-of-office BPs were normal. Conversely in patients with selective ambulatory or home BP elevations, office BP, although being below the hypertension values, was on average somewhat greater than in patients with in- and out-of-office BP normality. This may explain the cardiac structural abnormalities seen in these two conditions because it is well known that the relation between blood pressure and cardiovascular disease (and presumably organ damage) maintains a linearity also in the BP normality range. It does not entirely account for this phenomenon, however, because when in isolated office hypertension left ventricular mass index was adjusted for the increase in ambulatory or home values, its abnormality remained significant. This was the case also when in ambulatory hypertension left ventricular mass index was adjusted for the increase in office values. This allows speculation that in isolated office and ambulatory hypertension, cardiac structural abnormalities depend at least in part on neurohumoral or other factors unrelated to blood pressure values.

Finally, the cross-sectional nature of our study leads to two limitations. First, our data do not provide information on whether isolated office or ambulatory hypertension becomes less frequent with blood pressure measurements at follow-up visits. For isolated office hypertension this is not unlikely, because the “white coat” effect (the factor that is regarded to be importantly involved in the difference between office and ambulatory blood pressure values) shows some attenuation with time. We can thus not determine from the present study whether the presence or absence of cardiac structural alterations are related to, respectively, persistence or disappearance of these conditions. Second, we cannot infer from our findings what the increased incidence of cardiovascular morbidity and mortality in isolated office or ambulatory hypertension might be. However, left ventricular hypertrophy has been shown to carry an increased cardiovascular risk.
Therefore, it seems reasonable to ascribe a prognostic relevance to the greater prevalence of left ventricular hypertrophy that we observed and to suggest that the increased left ventricular mass and wall thickness that we have seen with isolated office and ambulatory hypertension may represent a marker of an abnormal increase in cardiac afterload.

References

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