Psychophysiological Reactivity and Cardiac End-Organ Changes in White Coat Hypertension

Carmine Cardillo, Francesco De Felice, Umberto Campia, and Giuseppe Folli

This study aimed 1) to assess whether patients with an exaggerated blood pressure response to the doctor’s presence (“white coat” effect) also display a pattern of enhanced blood pressure reactivity to mental stress and physical exercise and 2) to determine the presence of left ventricular structural and filling abnormalities in patients with white coat hypertension. We studied 56 (40 men) consecutive patients (mean [SD] age, 46.4 [9.1] years) whose clinic blood pressure was repeatedly high. Patients were classified as having white coat hypertension (n=20) if both their mean daytime (from 7 AM to 11 PM) ambulatory systolic and diastolic blood pressures were less than 134 and 90 mm Hg, respectively. Patients were considered to have persistent hypertension (n=36) if daytime systolic blood pressure was 134 mm Hg or more or diastolic blood pressure was 90 mm Hg or more. Eighteen subjects with clinic blood pressure lower than 140/90 mm Hg served as a normotensive control group. Blood pressure reactivity from baseline to mental arithmetic, isometric handgrip, and cycle ergometry did not display any difference among the three groups. The white coat hypertensive group had left ventricular mass index lower than the persistent hypertensive group but higher than the normotensive group. Doppler indexes of left ventricular diastolic filling displayed similar abnormalities in the white coat and persistent hypertensive groups compared with the normotensive group. We conclude that 1) we cannot distinguish white coat hypertensive patients by a pattern of blood pressure hyperreactivity to mental and physical laboratory tasks, and 2) white coat hypertension is characterized by mild cardiac enlargement and shares with persistent hypertension similar abnormalities in left ventricular filling. These latter findings suggest that white coat hypertension may not be considered an entirely innocuous clinical condition.

KEY WORDS • stress, psychological • exercise test • blood pressure • ventricular mass • ventricular function

Although clinic pressure reasonably predicts subsequent cardiovascular morbid events in hypertensive patients,1 24-hour ambulatory recording provides a more accurate assessment of cardiovascular risk.2 One possible explanation for this observation might be the “white coat” phenomenon, the exaggerated blood pressure rise related to the doctor’s visit,3 which may cause the misclassification of some normotensive subjects as hypertensive patients. Despite the long-standing recognition of white coat hypertension,4 some aspects of it are still unclear.5 In fact, there is no agreement about its prevalence, and the factors responsible for it are not clearly understood; moreover, its long-term prognostic significance has not been established, and consequently, whether it needs to be treated is unknown.

We hypothesized that patients who are normotensive during daily life and respond to the stress of a clinic visit with an exaggerated increase in blood pressure might have an exaggerated blood pressure rise also during exposure to other stressful situations. To test this hypothesis, we exposed a group of white coat hypertensive patients to a set of standardized mental and physical stressors and compared their responses with those of groups of normotensive subjects and of patients in whom hypertension was present both in the clinic and during daytime ambulatory recording, defined as having persistent hypertension.

Another aim of the present study was to assess the presence of hypertensive cardiac end-organ damage in patients with white coat hypertension. By virtue of their low ambulatory blood pressure values, white coat hypertensive patients are expected to be at low risk of cardiovascular sequelae, but repeated pressor episodes could eventually exert an adverse effect on the cardiovascular system, especially if the exaggerated pressor response to the clinic visit should be generalized to more regularly recurring stressful stimuli during daily life. To examine this aspect, we analyzed Doppler echocardiographic findings of left ventricular size and filling in white coat hypertensive patients and compared them with those of groups of normotensive subjects and persistent hypertensive patients.

Methods

Subject Population and Experimental Procedures

Fifty-six (40 men) consecutive mild-to-moderate essential hypertensive patients referred to our Hyperten-
Clinic took part in this study. Patients were classified as having hypertension if their clinic diastolic blood pressure (DBP) was persistently higher than 90 mm Hg. Clinic blood pressure was defined as the average of three sitting blood pressure readings taken after 5 minutes of rest on three different occasions during a 3-4 week period. Patients were eligible for this study if they had never been treated for hypertension or had their previous antihypertensive medications withdrawn for at least 6 months before screening. Patients were excluded if they had coronary, valvular, or other organic heart disease; obstructive lung disease or other chronic medical illnesses; or obesity and secondary hypertension. All patients had normal renal function, were on an unrestricted sodium diet, and were not performing regular aerobic exercise.

Eighteen subjects whose clinic blood pressure was repeatedly lower than 140/90 mm Hg were recruited from the hospital staff as a normotensive control group. All patients and subjects participated in the study on a voluntary basis after informed consent was obtained and the study protocol was approved by the local Institutional Review Board.

After the screening process, on separate days, patients and subjects underwent ambulatory blood pressure monitoring, laboratory stress testing, and Doppler echocardiography. Throughout the study, resting and stress testing systolic blood pressure (SBP) and DBP readings were obtained by the same observer (U.C.), who was unaware of the patient's clinical data, by use of a standard mercury manometer. DBP was generally recorded at phase V of the Korotkoff sounds, whereas during ergometry, Korotkoff phase IV was taken as the diastolic end point. Mean arterial pressure (MAP) was calculated according to the formula

\[ \text{MAP} = \text{DBP} + \left( \frac{(\text{SBP} - \text{DBP})}{3} \right) \]

Heart rate was recorded by electrocardiogram.

**Ambulatory Blood Pressure Monitoring**

Twenty-four-hour ambulatory blood pressure monitoring was performed by use of a portable, noninvasive recorder (SpaceLabs 90207, Redmond, Wash.), with the blood pressure cuff fitted on the nondominant arm. Monitoring was done on a typical workday, and subjects were encouraged to pursue their typical activities and to relax their arm at their side when the standard cuff inflated. Blood pressure recordings were done automatically at 15-minute intervals from 7 AM to 11 PM (daytime period) and at 20-minute intervals from 11 PM to 7 AM (nighttime period). The accuracy of the recorder was checked by performing three simultaneous readings with a standard mercury manometer through a Y-tube at the beginning and end of the monitoring session. On completion of the monitoring, data were analyzed by a computer program. In addition to the automatic editing criteria, additional criteria for deleting individual blood pressure readings included a pulse pressure that was less than 12 mm Hg or an inconsistent increase or decrease in SBP or DBP greater than 30 mm Hg from previous or subsequent readings. All recordings obtained in this study had at least 80% of the readings passing the deletion criteria. Subjects kept diaries of activities and emotions for aid in the editing process.

**Laboratory Stress Testing**

All psychophysiological examinations were carried out at approximately the same time in the morning (from 10 AM to noon), according to a protocol previously described. On arrival in a quiet laboratory room, subjects rested for 15 minutes in a sitting position, and then baseline (resting) blood pressure was obtained as the mean of three blood pressure readings within 5 minutes. Afterward, all subjects underwent the mental arithmetic test, the handgrip test, and the cycle ergometry test. The tests were always carried out in the same sequence, and before going on to the next test, subjects rested for a mean time of 15 minutes until blood pressure and heart rate returned to baseline. On a day preceding the experiments, the test protocols had been explained to the subjects and they had been made familiar with the investigational procedures.

The mental arithmetic test required each subject to subtract continuously the number 7 from a three-digit number as accurately and as quickly as possible for 3 minutes. Each subject performed the calculations aloud; throughout the test, wrong answers were immediately corrected and the experimenter continuously encouraged the subject to perform at maximum speed. The handgrip test was performed by use of a dynamometer. Subjects squeezed a rubber bulb connected to a gauge that displayed grip strength at 30% of predetermined voluntary maximal contraction for 3 minutes. They were instructed to count aloud during the test to avoid performing a Valsalva maneuver. The cycle ergometry test was a continuous stepwise test done with an electrical bicycle ergometer (Ergocard II, Ote Biomedica, Florence, Italy). Subjects started at a work load of 50 W for 5 minutes and then continued at 100 W for a further 5 minutes. To avoid adding any isometric component to this activity, subjects rested their hands on the handlebars.

During the mental arithmetic and handgrip tests, blood pressure and heart rate were recorded every minute, and during ergometry, in the last 30 seconds of each step. During the recovery phase after each test, circulatory measurements were done at 1-minute intervals.

**Doppler Echocardiography**

Echocardiograms were recorded using an Ultrasound Imaging System (model 77020A, Hewlett-Packard Co., Andover, Mass.) with a 2.5-MHz transducer. They were coded and read blindly by a skilled physician (F.D.) who was unaware of the subject's blood pressure or other clinical data. All M-mode studies were guided by two-dimensional echocardiogram with imaging in the left lateral decubitus position from the left parasternal window. End-diastolic measurements of left ventricular internal dimension (LVIDd), interventricular septum thickness, and posterior wall thickness were obtained at the R wave peak of the simultaneously recorded electrocardiogram following the recommendations of the American Society of Echocardiography and the Penn convention. Measurements made according to the recommendations of the Penn convention were used to calculate left
ventricular mass according to the anatomically validated formula of Devereux and Reichek. Measurements of left ventricular mass were divided by body surface area, calculated according to the method of Dubois, to obtain left ventricular mass index (LVMI). Measurements made according to the recommendations of the American Society of Echocardiography were used to calculate end-diastolic relative wall thickness as the ratio of posterior wall thickness to one-half left ventricular internal dimension. Cross-sectional area was calculated as previously described. Fractional shortening was calculated according to the formula

\[ FS(\%) = \left( \frac{LVIDd - LVIDs}{LVIDd} \right) \times 100 \]

where LVIDs is the systolic left ventricular internal dimension.

All measurements were computed as the average of at least five values for each parameter only on high-quality tracings on which the right and left sides of the interventricular septum and the endocardial and epicardial surfaces of the posterior left ventricular wall were recorded continuously throughout the cardiac cycle. Cardiac size indexes of two patients were excluded from analysis because of unsatisfactory echocardiographic tracings.

Pulsed-wave Doppler examination of the mitral valve was obtained from an apical view using a 2.5-MHz two-dimensional imaging and Doppler transducer with a sample volume aligned parallel to the expected transmural blood flow. The sampling started from the mitral annulus and moved toward the tips of the mitral leaflets searching for the highest velocity. To prevent the variability due to respiration, we averaged the values on at least five consecutive cardiac cycles. The following parameters were recorded: early transmitral peak flow velocity (E, centimeter per second), late diastolic (atrial) transmitral peak flow velocity (A, centimeter per second), and their ratio (E/A ratio).

**Statistical Analysis**

Data are generally expressed as mean (1 SD). The means of continuous variables were compared by one-way analysis of variance followed by Scheffé's test for multiple comparisons. Analysis of covariance was applied to identify possible confounding factors among anthropometric variables. Age was identified as a significant covariate for peak stress testing SBP, sex for measures of left ventricular size, and age for indexes of diastolic filling; therefore, these parameters were expressed as adjusted values. Frequencies were analyzed by \( \chi^2 \) statistic with Yates's correction and by Kruskal-Wallis test, as appropriate. Correlations were tested by univariate and multivariate linear regression analysis. All analyses were done with the SPSS/PC+ package on a microcomputer. The results were considered to be statistically significant at a value of \( p<0.05 \) (two-tailed).

Power calculations were done to assess whether adequate power was available to find clinically significant differences in the main variables of interest. Analyses showed that our sample size allowed detection with an 80% power, a 25% or greater difference among groups in SBP reactivity to laboratory tasks, and a 15% or greater difference among groups in Doppler echocardiographic variables.

Patients were classified as having white coat hypertension if both their mean daytime ambulatory SBP and DBP were less than 134 and 90 mm Hg, respectively. Patients were considered to have persistent hypertension if their daytime SBP was 134 mm Hg or more or their DBP was 90 mm Hg or more.

Cardiovascular reactivity during stress tests was expressed as peak stress testing SBP values (last minute of handgrip and ergometry, maximal blood pressure values during mental arithmetic) adjusted for resting SBP (average of the three baseline values) as a covariate. We reported only data concerning SBP reactivity, because DBP readings obtained with noninvasive techniques during stress testing may be inaccurate.

MAP was used instead of SBP and DBP in analyses of clinic-to-daytime blood pressure differences to reduce the number of statistical calculations.

**Results**

**Patient Classification and Demographic Features**

Of the 56 hypertensive patients eligible for this study, 20 (36%) were labeled as having white coat and 36 (64%) as having persistent hypertension. Table 1 reports demographic data of the three groups. Age was slightly but significantly greater in the persistent hypertensive group than in the normotensive group but was not different between the persistent and white coat hypertensive groups and between the white coat hypertensive and normotensive groups. No significant differences in sex distribution, body surface area, or resting heart rate were found among the three groups.

All hypertensive patients were examined for evidence of ocular end-organ damage by fundoscopy examination. Eye-fundus abnormalities were classified according to the criteria of Keith et al and coded as 0 (grade 0–1) and 1 (grade 2). No patient evidenced a retinopathy exceeding grade 2. Fundoscopy abnormalities were found in 15% of the white coat hypertensive group and in 39% of the persistent hypertensive group (\( p=0.140 \).
Clinic and Ambulatory Blood Pressures

Office and ambulatory blood pressure data are reported in Table 2. The clinic SBP and DBP values were significantly lower in the persistent hypertensive group (13.8 [7.9] mm Hg) than in the persistent hypertensive group (6.3 [7.1] mm Hg) (p<0.05). Similar findings were observed when clinic-to-daytime differences in SBP and DBP were analyzed. The percentage of hypertensive patients labeled as "hyperreactive" to the doctor's visit (white coat effect greater than the 95% upper confidence limit of the average clinic-to-daytime MAP difference observed in the whole hypertensive population) was significantly higher in the white coat hypertensive group (65%) than in the persistent hypertensive group (22%) (p<0.004). In the persistent hypertensive group, the percentage of hyperreactive patients was similar (p>0.05) to that of patients (19%) in whom MAP was higher during daytime monitoring than during clinic measurement (reverse white coat phenomenon). The reverse white coat phenomenon was observed in nine (50%) normotensive subjects.

Psychophysiological Testing

Blood pressure and heart rate values recorded during mental and physical stress testing are reported in Table 3. Mental arithmetic revealed higher SBP and DBP in the persistent and white coat hypertensive groups than in the normotensive group, and no significant difference was observed between the persistent and white coat hypertensive groups. The same pattern of blood pressure behavior was observed at peak of handgrip test and bicycle ergometry. Multiple stepwise regression analysis was used to determine the best predictors of peak stress testing SBP. Variables selected as predictors were age; sex; body mass index; resting, 24-hour, and daytime SBP; and LVMI. In all subjects, resting SBP was the major correlate of peak SBP during either mental arithmetic (partial r=0.89, p<0.001), handgrip test (partial r=0.81, p<0.001), or cycle ergometry (partial r=0.76, p<0.001). Age was an additional correlate for SBP during either mental stress (partial r=0.28, p=0.02), handgrip test (partial r=0.32, p=0.007), or cycle ergometry (partial r=0.28, p=0.02). Similar results were observed in the hypertensive subset.

As represented in Figure 2, SVP reactivity from resting values at peak of each task displayed no significant difference among the three groups. Adjusted SVP at peak of mental arithmetic test was 160.2 (9.9) mm Hg in the normotensive group, 166.1 (13.1) mm Hg in the white coat hypertensive group, and 166.6 (14.1) mm Hg in the persistent hypertensive group (all p>0.05). Adjusted SVP during handgrip test was 178.1 (15.4) mm Hg, 188.8 (18.4) mm Hg, and 182.5 (17.1) mm Hg in the normotensive, white coat, and persistent hyperten-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotension (1) (n=18)</th>
<th>White coat (2) (n=20)</th>
<th>Persistent (3) (n=36)</th>
<th>Analysis of variance</th>
<th>p 1 vs. 2</th>
<th>p 1 vs. 3</th>
<th>p 2 vs. 3</th>
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</thead>
<tbody>
<tr>
<td>Clinic SBP (mm Hg)</td>
<td>114.7 (9.1)</td>
<td>147.9 (13.3)</td>
<td>154.3 (13.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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</tr>
<tr>
<td>Clinic DBP (mm Hg)</td>
<td>75.4 (9.3)</td>
<td>97.6 (6.1)</td>
<td>102.7 (6.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Average 24-hour SBP (mm Hg)</td>
<td>109.5 (8.2)</td>
<td>120.6 (5.2)</td>
<td>139.4 (8.3)</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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<tr>
<td>Average 24-hour DBP (mm Hg)</td>
<td>73.6 (6.6)</td>
<td>82.2 (4.7)</td>
<td>95.2 (5.7)</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
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</tr>
<tr>
<td>Daytime SBP (mm Hg)</td>
<td>112.8 (8.7)</td>
<td>126.2 (7.3)</td>
<td>143.3 (9.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Daytime DBP (mm Hg)</td>
<td>77.8 (6.6)</td>
<td>87.7 (5.9)</td>
<td>98.9 (6.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
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<tr>
<td>Nighttime SBP (mm Hg)</td>
<td>100.2 (8.7)</td>
<td>106.3 (5.9)</td>
<td>129.4 (10.5)</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
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<tr>
<td>Nighttime DBP (mm Hg)</td>
<td>63.8 (7.8)</td>
<td>70.3 (5.5)</td>
<td>85.6 (7.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; daytime, 7 AM to 11 PM; nighttime, 11 PM to 7 AM. Values are mean (SD).
sive groups, respectively (all p>0.05). At peak of cycle ergometry, adjusted SBP was 193.6 (16.4) mm Hg, 207.4 (19.4) mm Hg, and 202.5 (18.1) mm Hg in the normotensive, white coat, and persistent hypertensive groups, respectively (all p>0.05).

In hypertensive patients, no correlation was observed between clinic-to-daytime blood pressure difference and SBP response induced by mental arithmetic (r=0.06, p=0.336), by handgrip test (r=0.05, p=0.365), and by cycle ergometry (r=0.07, p=0.297). SBP changes observed during mental stress showed a significant correlation with SBP increase induced by handgrip test (r=0.40, p=0.001) and by bicycle ergometry (r=0.37, p=0.002); SBP changes during handgrip and ergometry did relate to each other (r=0.24, p=0.04).

Because resting-to-task reactivity could have been influenced by the white coat effect on resting blood pressure values, we examined also daytime-to-task blood pressure reactivity by adjusting stress testing SBP values for daytime SBP as a covariate. Adjusted SBP at peak of mental arithmetic was significantly lower in the normotensive (142.3 [12.4] mm Hg) than in the white coat (174.1 [16.1] mm Hg) and the persistent (171.2 [21.1] mm Hg) hypertensive groups (both p<0.05), but the difference between the white coat and the persistent hypertensive groups was not statistically significant (p>0.05). Similarly, adjusted SBP at peak of handgrip test and cycle ergometry was significantly higher in the white coat (194.3 [22.4] and 213.2 [22.9] mm Hg, respectively) and the persistent (189.6 [23.3] and 205.1 [20.2] mm Hg, respectively) hypertensive groups than in normotensive subjects (157.3 [18.6] and 182.1 [17.7] mm Hg, respectively) (all p<0.05), and the difference between the two hypertensive groups was not statistically significant (both p>0.05).

**Doppler Echocardiographic Findings**

Table 4 reports Doppler echocardiographic data of the three groups. LVMi was significantly higher in the persistent hypertensive group than in the white coat hypertensive and normotensive groups, and the difference between the white coat hypertensive and normotensive groups was also statistically significant (Figure 3).

Interventricular septum, posterior, and relative wall thicknesses and cross-sectional area were significantly greater in the persistent hypertensive group than in the white coat hypertensive and normotensive groups, and a significant difference was also observed between the white coat hypertensive and normotensive groups. No significant difference in LVMI and fractional shortening was observed among groups.

Doppler studies of diastolic function revealed that the E/A ratio was significantly lower in the persistent and white coat hypertensive groups than in the normotensive group, and no significant difference was observed between the persistent and white coat hypertensive groups (Figure 4). The A component of left ventricular filling displayed no significant difference among groups. The A component was significantly higher in the persistent and white coat hypertensive groups than in the normotensive group, and no significant difference was observed between the white coat and persistent hypertensive groups.

Variables selected as predictors of LVMi in multiple regression analysis were age; weight; height; clinic, stress testing, 24-hour, daytime, and nighttime blood pressures; clinic-to-daytime blood pressure difference; and blood pressure changes associated with stress testing. For the whole group of subjects, clinic DBP was the major correlate of LVMi (partial r=0.57, p<0.001), whereas in the hypertensive subset the strongest correlate of LVMi was 24-hour DBP (partial r=0.34, p=0.011).

Variables selected to predict the E/A ratio were age, body surface area, resting heart rate, LVMi, and the different blood pressures. In all subjects, resting heart rate was the best predictor of the E/A ratio (partial r=0.38, p=0.002); age (partial r=0.36, p=0.003) and clinic SBP (partial r=0.32, p=0.008) were additional correlates. In the hypertensive subset, age was the major correlate of the E/A ratio (partial r=0.42, p=0.002).

**Different Definition Criteria for White Coat Hypertension**

In the absence of firm criteria for "normal" ambulatory blood pressure, to analyze whether the criterion of normalcy for daytime blood pressure used in this study...
could have affected the results, we reclassified hypertensive patients by setting three different cutoff points for normal daytime blood pressure. One discriminant point was set at 135/85 mm Hg and was derived from the consensus document on noninvasive ambulatory monitoring.16 Another discriminant point was set at 146/91 mm Hg and was derived from a meta-analysis of 23 studies using both invasive and noninvasive ambulatory recordings in clinical normotensive subjects or in general populations.17 Finally, because ambulatory SBP and DBP data of our study population were normally distributed, another cutoff point was derived from the mean+2 SD of daytime blood pressure recorded in our clinical normotensive group and was set at 130/91 mm Hg. The reclassifications resulted in a redistribution of the patients between the white coat and persistent hypertensive groups, but when the analyses were repeated using the new patient classifications, no substantial changes were seen in the results, as shown in Table 5.

Discussion

In the present study, 56 patients with persistently high clinic blood pressure readings were divided into white coat and persistent hypertensive groups according to the discriminant values of 134/90 mm Hg for daytime ambulatory blood pressure. The distinction between the two groups could not be made on clinical criteria, because the patients had comparable demographic characteristics and clinic blood pressure values. Obviously, ambulatory blood pressures were higher in the persistent than the white coat hypertensive group. The difference between clinic and ambulatory blood pressure values was higher in the white coat than in the persistent hypertensive group, but a few patients with persistent hypertension displayed a white coat effect as large as those with white coat hypertension.

Psychophysiological Reactivity

Our first hypothesis was that white coat hypertension could be characterized by a pattern of enhanced reactivity to a set of mental and physical laboratory stressors. We found that blood pressure response from baseline to mental arithmetic, handgrip test, and cycle ergometry was not higher in white coat than in persistent hypertensive patients and in normotensive subjects. Daytime-to-task blood pressure reactivity was lower in normotensive subjects than in clinical hypertensive patients, but it was not greater in the white coat than in the persistent hypertensive group. Our findings seem in agreement with the results of previous studies. Floras et al18 compared hypertensive patients whose difference between ambulatory and office MAP was greater than 10 mm Hg with patients whose clinic-to-daytime blood pressure difference was less than 10 mm Hg. They found that there was no difference between the two groups in blood pressure increase during mental arithmetic and that blood pressure rise induced by bicycle exercise was higher in patients whose cuff measurements accurately reflected ambulatory readings. Siegel et al19 reported that blood pressure reactivity to treadmill exercise and to a set of mental tasks was similar for white coat and persistent hypertensive patients. Julius et al20 found that patients with white coat hypertension were not hyper-responders to the stress of mental arithmetic or to isometric exercise. Moreover, different studies have demonstrated that white coat hypertensive patients do not have an enhanced blood pressure variability, as reflected both by the standard deviation of ambulatory blood pressure18,19 and by home-work blood pressure difference.13 All these findings are consistent with the hypothesis that the white coat phenomenon is a specific effect on blood pressure related to the clinic setting rather than a manifestation of a generalized hyperreactivity. This seems further confirmed by the lack of
correlation between clinic-to-daytime blood pressure difference and blood pressure changes from baseline induced by the laboratory tasks in hypertensive patients of our study. The discrepancy between blood pressure response to the doctor's visit and to laboratory stressors may be due to the different psychophysiological mechanisms responsible for them. Anger and anxiety, which are involved in modulating blood pressure reactivity to laboratory stressors,21 do not seem to play a major role in the white coat phenomenon. Recent studies have shown that patients with white coat hypertension do not score higher on reactivity scales measuring anger, anxiety, or the intensity of emotions experienced in stressful situations.19,20,22 Pickering et al13 observed that clinic-to-daytime blood pressure difference was higher in hypertensive patients than in normotensive subjects, a finding confirmed by our data. They hypothesized that the white coat effect could be a learned, conditioned response, in which fear originally induces an increase in blood pressure and, subsequently, the awareness of hypertension determines an increased sympathetic arousal so that blood pressure remains high over repeated visits. This hypothesis seems supported by the observation of Rostrup et al,23 who found that awareness of hypertension may induce per se an increase in sympathetic activity and reactivity to stress. However, the findings of Julius et al,20 who reported that white coat hypertensive patients had elevated clinic blood pressure already in childhood, an age when the individual does not yet understand the risk and meaning of an elevated blood pressure, depose against this view.

Cardiac End-Organ Changes

Another aim of the present study was to assess the presence of cardiac end-organ involvement in patients with white coat hypertension. We found that the white coat hypertensive group had LVMI intermediate between normotensive subjects and persistent hypertensive patients. Doppler indexes of diastolic left ventricular filling were equally modified in the white coat and persistent hypertensive groups compared with the normotensive group. There are some differences between our findings and those of a previous study from White et al.24 They

![FIGURE 3. Plots show values of left ventricular mass index (LVMI) in patients of normotensive (NT) group (●), white coat hypertensive (WCH) group (○), and persistent hypertensive (PH) group (▲). Horizontal bars represent mean value of each group. *p<0.05 vs. NT, #p<0.05 vs. WCH.](image)

![FIGURE 4. Plots show values of the ratio of early transmitral flow velocity (E) to atrial transmitral flow velocity (A) of ventricular diastolic filling in patients of normotensive (NT) group (●), white coat hypertensive (WCH) group (○), and persistent hypertensive (PH) group (▲). Horizontal bars represent mean value of each group. *p<0.05 vs. NT.](image)
white coat hypertensive patients. This discrepancy might be due to the different techniques used in the two studies where there was no difference in the E peak between hypertensive groups. This finding supports the concept of pathophysiological similarities between patients with clinical hypertension.33

In our study, we could have assigned to the white coat group patients with reduced A peak or an opposite pattern, respectively. This means that, in hypertensive patients, a greater proportion of left ventricular filling occurred late rather than early in diastole, probably because of an abnormal left ventricular relaxation. We observed that abnormalities of left ventricular diastolic filling were similar in both hypertensive groups. This finding supports the concept of pathophysiological similarities between patients with white coat and persistent hypertension, which are not dependent on ambulatory blood pressure values. Our data seem consistent with previous observations of an altered E/A ratio already present in very mild forms of hypertension,24 in young borderline essential hypertensive patients,22 and even before the development of true clinical hypertension.23

Limitations

A potential limitation of all studies using arbitrary cutoff points to categorize patients is the possibility of a selection bias causing the mislabeling of some patients. This hypothesis seems further supported by the findings of a recent study from Verdecchia et al.26 They demonstrated that left ventricular mass and filling features are similar in normotensive subjects and white coat hypertensive patients when conservative definition criteria for normotensive subjects are used so that 24-hour and daytime blood pressure values are not different in the two groups. On the other hand, left ventricular involvement becomes evident in white coat hypertensive patients when the use of less strict criteria makes ambulatory blood pressure higher in this group than in normotensive subjects. Our finding of mild cardiac structural changes in white coat hypertension seems consistent with the results of Julius et al.27 who reported that white coat borderline hypertensive patients have increased minimal vascular resistance, an index of structural vascular changes.28

Again, in contrast with our results, White et al24 reported that radionuclide-measured rapid left ventricular filling was significantly reduced in persistent but not in white coat hypertensive patients. This discrepancy might be due to the different techniques used in the two studies to assess cardiac diastolic function. In our study, we used Doppler echocardiography, which offers the advantage over other noninvasive techniques of providing information about the transmitral flow velocities that is dependent on pressure–flow interactions.29 Stoddard et al.30 have recently suggested that abnormalities in left ventricular stiffness or relaxation may have different influences on Doppler filling pattern, inducing an enhanced E peak with reduced A peak or an opposite pattern, respectively. The decreased E/A ratio observed in both hypertensive groups of our study was due to an increased A peak, whereas there was no difference in the E peak between hypertensive patients and normotensive subjects. This means that, in hypertensive patients, a greater proportion of left ventricular filling occurred late rather than early in diastole, probably because of an abnormal left ventricular relaxation.

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### Table 5. Peak Stress Testing Systolic Blood Pressure (SBP) Values Adjusted for Resting SBP and Main Doppler Echocardiographic Findings According to Different Discriminant Values for Daytime Ambulatory Blood Pressure

<table>
<thead>
<tr>
<th>Cutoff point</th>
<th>Variable</th>
<th>Normotension (1)</th>
<th>White coat (2)</th>
<th>Persistent (3)</th>
<th>Analysis of covaraiance</th>
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<tbody>
<tr>
<td>135/85 mmHg</td>
<td>Mental task SBP (mm Hg)</td>
<td>18</td>
<td>158.3 (10.3)</td>
<td>27</td>
<td>166.5 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Handgrip SBP (mm Hg)</td>
<td>18</td>
<td>177.4 (16.1)</td>
<td>27</td>
<td>184.1 (19.7)</td>
</tr>
<tr>
<td></td>
<td>Ergometry SBP (mm Hg)</td>
<td>18</td>
<td>191.5 (17.4)</td>
<td>27</td>
<td>202.8 (20.7)</td>
</tr>
<tr>
<td></td>
<td>LVMI (g/m²)</td>
<td>18</td>
<td>81.9 (16.5)</td>
<td>25</td>
<td>108.4 (19.2)</td>
</tr>
<tr>
<td></td>
<td>E/A ratio</td>
<td>18</td>
<td>1.32 (0.37)</td>
<td>27</td>
<td>1.07 (0.29)</td>
</tr>
<tr>
<td>146/91 mmHg</td>
<td>Mental task SBP (mm Hg)</td>
<td>18</td>
<td>158.3 (10.3)</td>
<td>43</td>
<td>166.4 (15.4)</td>
</tr>
<tr>
<td></td>
<td>Handgrip SBP (mm Hg)</td>
<td>18</td>
<td>177.4 (16.1)</td>
<td>43</td>
<td>185.9 (17.8)</td>
</tr>
<tr>
<td></td>
<td>Ergometry SBP (mm Hg)</td>
<td>18</td>
<td>191.5 (17.4)</td>
<td>43</td>
<td>204.7 (19.6)</td>
</tr>
<tr>
<td></td>
<td>LVMI (g/m²)</td>
<td>18</td>
<td>81.9 (16.5)</td>
<td>41</td>
<td>112.4 (22.7)</td>
</tr>
<tr>
<td></td>
<td>E/A ratio</td>
<td>18</td>
<td>1.32 (0.37)</td>
<td>43</td>
<td>1.03 (0.28)</td>
</tr>
<tr>
<td>130/91 mmHg</td>
<td>Mental task SBP (mm Hg)</td>
<td>18</td>
<td>158.3 (10.3)</td>
<td>20</td>
<td>166.1 (15.4)</td>
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<td>105.3 (16.6)</td>
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<td>E/A ratio</td>
<td>18</td>
<td>1.32 (0.37)</td>
<td>20</td>
<td>1.07 (0.29)</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; LVMI, left ventricular mass index; E, early peak flow velocity; A, late (atrial) peak flow velocity.
suggested by the observations that blood pressure hyperreactivity to the clinic setting was not specific to the white coat hypertensive group, being also present in some patients of the persistent hypertensive group, and that white coat hypertensive patients had ambulatory pressure higher than normotensive subjects. However, the results were not substantially modified by changing ambulatory blood pressure discriminant values. Moreover, in hypertensive patients, ambulatory blood pressure was linearly related to LVMI, which seems to make these findings not dependent on the choice of the partition values.

The main limitation of this study is its cross-sectional design, which does not enable us to obtain any information about the prognostic significance of cardiac structural and filling abnormalities observed in white coat hypertension. It has been shown that echocardiographically detected left ventricular hypertrophy is an independent risk factor for cardiovascular complications in hypertensive patients,46 but the prognostic value of mild increases in left ventricular mass and of a decreased E/A ratio is still unknown.

Conclusions

This study indicates that, although its pathophysiology remains unclear, white coat hypertension is not a part of a larger pattern of hyperresponsiveness to psychophysiological stimuli. On the other hand, it is associated with left ventricular structural and filling abnormalities, suggesting that it could not be considered an entirely innocuous clinical condition. Until a prospective follow-up will not correctly evaluate cardiovascular risk associated with white coat hypertension, the assessment of target-organ status and a better understanding of factors involved in its early changes, rather than the definition of "normalcy" for ambulatory blood pressure values, seem helpful in the clinical management of such patients.

References

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C Cardillo, F De Felice, U Campia and G Folli

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