Background: Isolated office (IO) hypertension is a benign condition according to some researchers, whereas others believe it is associated with cardiovascular abnormalities and increased cardiovascular risk. The aim of this study is to compare morphofunctional characteristics of the left ventricle (LV) in IO hypertensive subjects, normotensive subjects (hereafter, hypertensives and normotensives), and never-treated sustained hypertensives. The 3 groups were matched not only by age, sex, and body mass index but also by clinic blood pressure (BP) (IO hypertensives and sustained hypertensives) and daytime BP (IO hypertensives and normotensives).

Methods: We enrolled 42 IO hypertensives (clinic BP >140 and/or 90 mm Hg and daytime BP ≤130/80 mm Hg), 42 sustained hypertensives (clinic BP >140 and/or 90 mm Hg and daytime BP ≥140 and/or 90 mm Hg) and 42 normotensives (clinic BP <135 and/or 85 mm Hg and daytime BP ≤130/80 mm Hg). Left ventricular morphologic features and function were assessed using digitized M-mode echocardiography.

Results: Compared with normotensives, IO hypertensives had significantly thicker LV walls, increased LV mass, reduced diastolic function, increased prevalence of LV hypertrophy, and preclinical diastolic dysfunction. Sustained hypertensives, compared with IO hypertensives, had significantly thicker LV wall, higher LV mass, and lower diastolic function, whereas the prevalence of LV hypertrophy and preclinical diastolic dysfunction was greater than in IO hypertensives, but the difference did not reach statistical significance (P = .29).

Conclusions: Comparing matched BP groups, IO hypertensives have LV morphofunctional characteristics considerably different from normotensives and qualitatively similar to sustained hypertensives. Therefore, our results support the hypothesis that IO hypertension should not be considered as simply a benign condition.

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ISOLATED OFFICE (IO) hypertension, also defined as “white-coat” hypertension, is a frequently diagnosed condition characterized by persistently elevated office blood pressure (BP) combined with normal daytime ambulatory BP.1,2 The incidence of this condition is 12% to 50%, depending on the definition of IO hypertension used and the population studied.3,4 The literature remains inconclusive on the issue of whether IO hypertension carries a pathological risk: it is considered an essentially benign condition by some researchers5–10 and a pathological situation, potentially associated with cardiovascular risk, by others.11–19 There is general agreement that compared with sustained hypertensives, IO hypertensives have substantially less target organ damage and cardiovascular risk.5–9,14,17,20,21 However, compared with normotensives, IO hypertensives show some degree of cardiovascular abnormality, as in many,12–19,22 but not all,5,6,8,9 similar studies.

Many factors can account for the discrepancies between results. Besides differences in age and body mass index (BMI) in the groups compared, a major role is played by the use of different daytime BP criteria for defining IO hypertension and by the enrollment of hypertensives previously treated with antihypertensive drugs that can, per se, modify cardiovascular characteristics. Moreover, an important source of bias is the limited BP comparability among groups: often, IO hypertensives have clinic BPs lower than sustained hypertensives and ambulatory BPs within the reference range but substantially higher than normotensives.

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PARTICIPANTS AND METHODS

PARTICIPANTS

The patients enrolled had been selected from among 438 hypertensives never treated with antihypertensive drugs, referred in 2 years (1997-1999) to our outpatient hypertension clinic (Division of Internal Medicine, University of Insubria, Varese, Italy) because of office BPs repeatedly (>4 visits in 4 months) higher than 140 and/or 90 mm Hg. We enrolled 42 IO hypertensives (18 men and 24 women; mean ± SD age, 42 ± 6 years; mean ± SD BMI [calculated as weight in kilograms divided by the square of height in meters], 25.3 ± 2.7) and 42 sustained hypertensives individually matched by sex, age (within 1 year), BMI (within 1.0 kg/m²), and mean clinic BP (within 3 mm Hg). The major selection criteria were an LV M-mode echocardiogram of good quality; no clinical, electrocardiographic, or echocardiographic evidence of heart failure, myocardial infarction, aortic or congenital or valvular heart diseases; and no systemic diseases, such as diabetes mellitus or connective tissue disorders, which could induce changes in LV structure and function. From a survey of the hospital staff, we recruited 42 normotensives, individually matched with IO hypertensives by sex, BMI, and mean daytime BP. None of the participants were receiving any medications.

Mean clinic BP for the matching was obtained by averaging BP values taken during 2 visits that were 1 week apart. During each visit, the same operator, using a mercury sphygmomanometer, measured BP 3 times at 10-minute intervals with patients in the sitting position after a 20-minute rest. We defined patients as IO hypertensive when clinic BP was greater than 140 and/or 90 mm Hg and daytime BP was 130/80 mm Hg or less; as sustained hypertensive when clinic BP was greater than 140 and/or 90 mm Hg and daytime BP was 130/80 mm Hg or less; and as normotensive when clinic BP was less than 135/85 mm Hg and daytime BP was 130/80 mm Hg or less.

This study was approved by the ethical committee of the Department of Clinical and Biological Sciences, University of Insubria, and all the participants gave informed consent.

ECHOCARDIOGRAPHIC EXAMINATION

Echocardiographic examination was performed using a Hewlett-Packard Sonos 1500 echograph (Hewlett-Packard, Andover, Mass) with a 2.0/2.5-MHz transducer. Left ventricular M-mode echocardiograms were recorded under 2-dimensional control, at a paper speed of 100 mm/s, and an electrocardiogram was performed simultaneously. The M-mode tracings were evaluated by a single masked operator (A.M.G.) who digitized 4 consecutive cardiac cycles of each echocardiogram, as originally described by Upton and Gibson, using a Numonics 2205 graphic tablet (Numonics, Montgomeryville, Pa). A personal computer was used to process digitized data, averaging the 4 cardiac cycles. We evaluated LV end-diastolic diameter, end-diastolic thickness of the interventricular septum and posterior wall, LV mass according to the Penn convention, LV mass index (LV mass normalized for body surface area), percentage fractional shortening of LV diameter, peak shortening rate of LV diameter, peak lengthening rate of LV diameter, and peak thinning rate of the LV posterior wall.

The reference ranges of the laboratory variables were derived from the evaluation of 200 healthy adults; the upper reference limits for LV mass index were 130 g/m² for men and 110 g/m² for women. The reproducibility of the echocardiographic measurements have been tested on 20 healthy individuals (each examined 3 times by using the same ultrasonic technique); the same operator digitized 4 consecutive cardiac cycles of each echocardiogram. The coefficients of variation were as follows: LV end-diastolic diameter, 0.4%; septal thickness, 3.2%; posterior wall thickness, 3.4%; peak shortening rate, 1.1%; peak lengthening rate, 4.7%; and peak thinning rate, 7.3%.

24-HOUR AMBULATORY BP MONITORING

Noninvasive ambulatory BP monitoring was performed using a portable automated Takeda TM 2421 ambulatory BP monitor (Takeda, Osaka, Japan), and 24-hour heart rate monitoring was performed simultaneously. The unit was set to take readings every 15 minutes throughout the 24 hours. The following variables were evaluated: mean 24-hour, daytime (7 AM to 10 PM), and nighttime (10 PM to 7 AM) systolic and diastolic BP and heart rate and nocturnal decline (percentage) in systolic and diastolic BP.

STATISTICAL ANALYSIS

Statistical evaluation of the results was performed using analysis of variance, followed by the Scheffé test. The chi² test was used to compare differences in prevalence among groups. Values are expressed as mean ± SD; P < .05 was considered statistically significant.

Therefore, we compared the morphofunctional characteristics of the left ventricle (LV) in IO hypertension, normotension, and never-treated sustained hypertension, selecting 3 groups of individuals carefully matched not only by age, sex, and BMI but also by clinic BP (IO hypertensives and sustained hypertensives) and daytime BP (IO hypertensives and normotensives).

RESULTS

As a consequence of selection criteria, the 3 groups were comparable in age, sex, waist-hip ratio, and BMI; clinic BP was nearly identical in IO hypertensives and sustained hypertensives and significantly higher than in normotensives (P < .001). Ambulatory BP was nearly identical in IO hypertensives and normotensives and significantly lower than in sustained hypertensives (P < .001) (Table 1). The 3 groups were of comparable socioeconomic status.

Left ventricular end-diastolic diameter was normal (<56 mm) in all participants and was not significantly different among the 3 groups, whereas septal and posterior wall thickness increased significantly from normotensives to IO hypertensives to sustained hypertensives (Table 2) (P < .001). Left ventricular hypertrophy (LV mass index > 130 g/m² in men and > 110 g/m² in women) was found in 7 IO hypertensives (17%; P = .03 vs normotensives) and in 17 sustained hypertensives.
Percentage fractional shortening and peak shortening rate of LV diameter—indices of LV systolic function—were normal (30% and 1.9 s⁻¹, respectively) in all participants and similar among the 3 groups (Table 2). Left ventricular diastolic function was impaired (peak lengthening rate of LV diameter = 3.6 s⁻¹ and/or peak thinning rate of the LV posterior wall = 8.4 cm/s) in 11 IO hypertensives (26%; P = .005 vs normotensives) and in 19 sustained hypertensives (45%; P = .29 vs IO hypertensives). Mean values of both diastolic indices decreased significantly from normotensives to IO hypertensives to sustained hypertensives (Table 2) (P < .001).

To our knowledge, this is the first study on LV characteristics in IO hypertension that compares IO hypertensives with normotensives and sustained hypertensives matched not only by sex, age, and BMI but also by mean clinic BP (IO hypertensives and sustained hypertensives) and mean daytime BP (IO hypertensives and normotensives). By using this design, we avoid important sources of bias, represented by IO hypertensives hav-
ing clinic BPs higher than normal but substantially lower than those of sustained hypertensives and, above all, daytime BPs within the reference range but substantially higher than those of normotensive controls. In the latter condition, because a BP even slightly higher than normal may result in a severe increase in the hemodynamic load of the heart, differences in LV characteristics between IO hypertensives and normotensives could be related to differences in daytime ambulatory BP rather than to IO hypertension. Another factor that affects the outcome of studies of IO hypertension is the cutoff BP value selected for daytime BP normality: higher daytime values lead to higher prevalence of IO hypertension and greater prevalence of LV changes in this condition. Many studies that found cardiovascular changes in IO hypertensives similar to those in sustained hypertensives and significantly different from those in normotensives used a daytime BP cutoff value of 140/90 mm Hg or higher. This criterion has been questioned recently: this value is probably too high, leading to sustained hypertensives similar to those in sustained hypertensives, and it has been suggested that a restrictive definition (daytime BP ≤130/80 mm Hg) is more reliable for diagnosing IO hypertension. In our study, to reliably compare true IO hypertensives and true sustained hypertensives, we chose the restrictive cutoff value of 130/80 mm Hg as the upper normal daytime BP for defining IO hypertension and the value of 140/90 mm Hg as the lower daytime BP for sustained hypertension. Finally, we enrolled only individuals never treated with antihypertensive drugs to avoid the possible effect of previous treatments on LV characteristics.

Following the previously mentioned criteria, we studied 3 groups that were almost identical in age, sex, BMI, mean clinic BP, and mean daytime BP. Our main finding is that IO hypertensives have LV morphofunctional changes qualitatively similar to sustained hypertensives but of lesser extent. In fact, compared with normotensives, IO hypertensives had significantly thicker LV walls, increased LV mass, a higher prevalence of LV hypertrophy, decreased diastolic function, and a higher prevalence of preclinical diastolic dysfunction. Sustained hypertensives, compared with IO hypertensives, had significantly thicker LV wall, higher LV mass, and lower diastolic function, whereas the prevalence of LV hypertrophy and preclinical diastolic dysfunction was greater than in IO hypertensives, but the difference did not reach statistical significance (P = .29). Left ventricular end-diastolic diameter was normal in all participants and almost identical in the 3 groups; therefore, the difference in LV mass index was due to the progressively increased thickness of the interventricular septum and the posterior wall from normotensives to IO hypertensives to sustained hypertensives, indicating a predominant concentric pattern of hypertrophy. As a consequence of selection criteria, the differences in LV characteristics among normotensives, IO hypertensives, and sustained hypertensives were not accounted for by differences in age, sex, BMI, clinic BP, or ambulatory BP.

Considering the data from the literature, our finding of increased LV mass in IO hypertension is in agreement with many, whereas all authors agree in reporting a normal LV systolic function, as we have found in our group of IO hypertensives. Left ventricular diastolic function in IO hypertension has been evaluated in few studies, using different methods and reaching different conclusions: compared with normotensives, diastolic function has been found to be normal reduced but not significantly or significantly decreased. We evaluated LV diastolic function by means of peak lengthening rate and peak wall thinning rate, both derived from digitized M-mode echocardiograms. These indices, less used than Doppler-derived variables, are more sensitive in discriminating between normal and impaired diastolic function in the presence of myocardial hypertrophy; they are also less affected by heart rate and events occurring during isovolumic relaxation. As noted previously, IO hypertensives had diastolic indices significantly lower than normotensives and higher than sustained hypertensives; moreover, the prevalence of preclinical diastolic dysfunction, significantly higher in IO hypertensives than in normotensives, was greater in sustained hypertensives, but the difference between sustained hypertensives and IO hypertensives did not reach statistical significance. It is well known that in hypertension, LV diastolic dysfunction is an early finding, often preceding the development of detectable LV hypertrophy: the same pattern is followed in IO hypertension, as demonstrated by our finding of a prevalence of diastolic dysfunction greater than the prevalence of LV hypertrophy in IO hypertensives and sustained hypertensives.

Our study does not explain the underlying mechanism leading to the development of LV changes in IO hypertension, but it may be speculated that transient BP increases, caused by exaggerated responses to mild stress, such as during medical evaluation, may have an effect on cardiac growth, leading to hypertrophy. One study in dogs showed that concentric LV hypertrophy can be produced by intermittent compression of the dogs’ limbs to increase BP. Furthermore, experimental studies have shown that brief episodes of cardiac pressure overload are sufficient to induce growth-related genes and protein synthesis in the heart.

Left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality; therefore, taken together, the findings of increased LV mass and decreased diastolic function indicate that IO hypertension confers an increased cardiovascular risk, also when the diagnosis of IO hypertension is based on a restrictive cutoff value for normal daytime BP.

Recently, Muldoon et al., matching individuals on the basis of clinical and daytime BP, reached similar results regarding carotid artery changes: carotid artery involvement (increased intima media thickness and plaque index) was greater in IO hypertensives than in normotensives and was similar to that in sustained hypertensives.

In conclusion, IO hypertension, defined on the basis of a restrictive value for normal daytime BP, is associated with LV morphofunctional changes similar, at least qualitatively, to those found in never-treated sustained hypertensives. In fact, in strictly BP-matched groups, IO hypertensives have increased LV mass and decreased LV diastolic indices compared with normotensives, with sus-
tained hypertensives having higher LV mass and lower diastolic function compared with IO hypertensives. These differences are not accounted for by differences in age, sex, BMI, clinic BP, or ambulatory BP. Therefore, the results of this study support the hypothesis that IO hypertension should not be simply considered a benign condition; further studies are needed to determine whether longitudinal monitoring and nonpharmacological interventions are enough or whether IO hypertensives with demonstrated cardiovascular remodeling also need drug treatment.

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