

ORIGINAL ARTICLE

Isolated office hypertension: A 3-year follow-up study

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Abstract

The study aimed to evaluate, over a 3-year period, the progression towards sustained hypertension and left ventricular (LV) changes in patients with isolated office (IO) hypertension (office BP > 140 and/or 90 mmHg, daytime BP < 130/80 mmHg). After 3 years from the basal evaluation, 38 subjects with basal normal BP and 42 subjects with basal IO hypertension underwent a second 24-h BP monitoring and echocardiography; 19 patients of the basal IO hypertension group were not reevaluated because they had already developed ambulatory hypertension and were on antihypertensive treatment. At the second evaluation, the 38 normotensive subjects had unchanged BP and LV parameters; 25 IO hypertensives have developed sustained hypertension. Considering them together with the 19 patients already treated, 72% of 61 IO hypertensives developed ambulatory hypertension over a 3-year period. The patients who subsequently developed hypertension differed from the group who did not only for lower basal values of LV diastolic parameters; all the patients with basal LV hypertrophy and/or preclinical diastolic impairment subsequently developed sustained hypertension. In conclusion, IO hypertensive patients show a high rate of progression towards sustained hypertension. Basal LV hypertrophy and/or preclinical diastolic dysfunction were the only markers of a greater risk of becoming hypertensives.

Key Words: *Ambulatory BP monitoring, diastolic function, isolated office hypertension, left ventricular hypertrophy*

Introduction

Isolated office (IO) hypertension, also defined as “white-coat” hypertension, is characterized by persistently elevated office blood pressure (BP) and normal daytime ambulatory BP (1). The correct characterization of IO hypertension has several clinical implications, the most important being to avoid the prescription of unnecessary antihypertensive therapy and to identify subjects who are probably at an increased cardiovascular risk compared with normotensive population. In fact, whereas some authors regard IO hypertension as a benign condition (2–4), others have found it associated with a prevalence of target organ damage lower than sustained hypertension, but significantly higher than in normotensive subjects (5–9). Moreover, an increased incidence of cardiovascular events has been demonstrated in patients with IO

hypertension compared with normotensive subjects (10–12). The few studies that evaluated if IO hypertension represents a transient state towards sustained hypertension, obtained conflicting results: a high rate of progression to sustained hypertension (74%) (13), a lower rate (37%) (14), or a rate of progression similar to that found in normotensive controls (11%) (15). Moreover it is still not known if some characteristics, such as BP values or presence of target organ damage, could be a prognostic indicator of the development of sustained hypertension.

Therefore, we have considered it of interest to evaluate, over a 3-year period, the rate of progression towards sustained hypertension and the changes in left ventricular (LV) morpho-functional characteristics in a group of patients with never-treated IO hypertension, looking also for basal demographic, BP or LV characteristics that could possibly predict

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the development of sustained hypertension. We also evaluated over the same 3-year period a group of normotensive subjects.

Material and methods

For a previous study (8), we selected subjects with normal BP (office BP < 140/90 mmHg and daytime BP < 130/80 mmHg) and subjects with IO hypertension, defined as office BP repeatedly > 140 and/or 90 mmHg (four or more measurements in 4 months) and daytime BP < 130/80 mmHg. Other selection criteria were as follows: no previous antihypertensive treatment, LV M-mode echocardiogram of good quality; no clinical, electrocardiographic or echocardiographic evidence of heart failure, coronary artery disease or valvular heart diseases; no systemic diseases, such as diabetes mellitus or connective tissue disorders, which could influence *per se* LV structure and function.

After at least 3 years from the basal evaluation, we called back the IO hypertensive patients and the normotensive subjects. Of the normotensive group (basal evaluation: 56 subjects) it was possible to contact 48 subjects and 38 agreed to be reevaluated (Figure 1). Among the IO hypertensive patients (basal evaluation: 79 subjects) it was possible to contact 72 subjects: 11 refused to undergo the second evaluation, 19 patients have already developed ambulatory hypertension (diagnosed by means of 24-h BP monitoring) and were on chronic antihypertensive treatment; therefore we reevaluated 42 subjects, all still not treated with antihypertensive drugs (Figure 1).

Each patient underwent a 24-h ambulatory BP monitoring and an echocardiographic examination. Mean clinic BP was obtained by averaging BP values taken during two visits, 1 week apart; during each visit, the same operator, using a mercury sphygmomanometer, measured BP three times at 10-min intervals with the patient in the sitting position, after a 20-min rest. The study was approved by the Ethical Committee of the Department of Clinical Medicine and all the subjects gave their informed consent.

Non-invasive 24-h ambulatory BP monitoring

Non-invasive 24-h ambulatory BP monitoring was performed with a portable automated Takeda TM 2421 and simultaneous 24-h heart rate monitoring was obtained. The unit was set to take readings every 15 min throughout the 24 h. The

following parameters were evaluated: mean 24-h, daytime (from 07.00 to 22.00 h) and night-time (from 22.00 to 07.00 h) systolic and diastolic BP and heart rate.

Echocardiographic examination

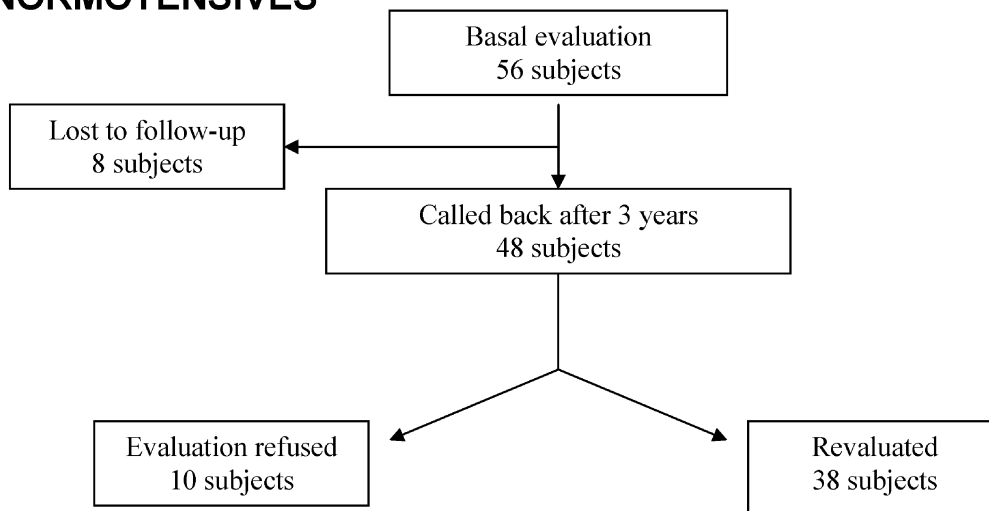
The echocardiographic examination was performed by the same operator who did the basal evaluation, using a Hewlett-Packard Sonos 5500 with a 2.0/2.5 MHz transducer. LV M-mode echocardiograms were recorded under two-dimensional control, at a paper speed of 100 mm/s, with a simultaneous electrocardiogram. A single operator, unaware of the clinical characteristics of the patients, evaluated the M-mode tracings, digitizing four consecutive cardiac cycles of each echocardiogram, as originally described by Upton & Gibson (16), using a Numonics 2205 graphic tablet. An IBM personal computer processed digitized data, averaging the four cardiac cycles. We evaluated LV end-diastolic diameter, end-diastolic thickness of interventricular septum and posterior wall, LV mass (17), peak shortening rate of LV diameter, peak lengthening rate of LV diameter and peak thinning rate of LV posterior wall. LV mass was normalized for body surface area. The normal limits of the parameters in our laboratory have been derived from the evaluation of 200 normal adults. The reproducibility of the echocardiographic measurements has been tested on 20 normal subjects (each examined three times by the same ultrasonic technique); the same operator digitized four 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%, peak thinning rate 7.3%.

Mitral inflow velocities were evaluated by pulsed-wave Doppler with the sample volume placed at the tips of the mitral leaflets, from the apical four-chamber view. Using the average of 5 beats for the analysis, we measured the ratio between peak early transmitral flow velocity (E) and peak late transmitral flow velocity (A) (E/A ratio), and the deceleration time of E velocity (DT, time from peak E velocity to the time when E wave descent intercepted the zero line).

Statistical analysis

The results have been evaluated using analysis of variance (ANOVA), paired and unpaired Student's *t*-tests as needed. The data are presented as

NORMOTENSIVES



ISOLATED OFFICE HYPERTENSIVES

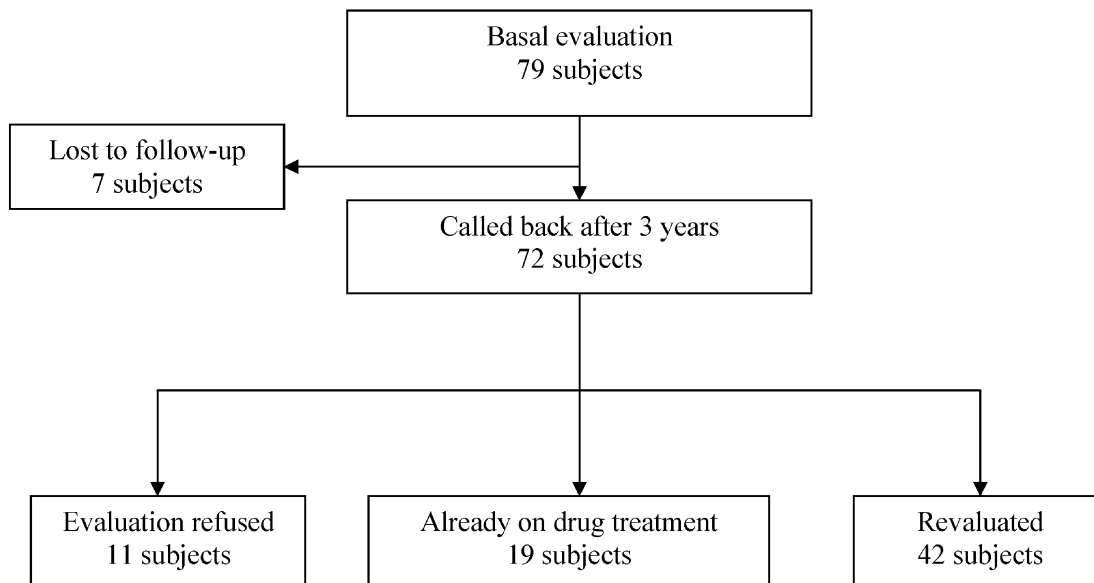


Figure 1. Flowchart of the study population.

mean ± standard deviation; a *p*-value <0.05 was considered statistically significant.

Results

At the basal evaluation IO hypertensive subjects were not significantly different from the

normotensive control group with regard to gender (men/women normotensive group 15/23, IO hypertensives 18/24, ns) age, body mass index and 24-h BP values (Tables I and II).

At the second evaluation, at least 3 years after the basal study, all the 38 subjects with basal normal BP were still normotensive, with clinic and 24-h BP

Table I. Clinical and left ventricular (LV) morpho-functional characteristics of the 38 normotensive subjects.

	Basal	P	2nd evaluation
Age, years	43 ± 5	<0.001	46 ± 5
BMI, kg/m ²	25.6 ± 2.1	ns	25.5 ± 2.2
Clinic SBP, mmHg	122 ± 7	ns	121 ± 5
Clinic DBP, mmHg	75 ± 6	ns	73 ± 8
24-h SBP, mmHg	120 ± 6	ns	118 ± 7
24-h DBP, mmHg	70 ± 5	ns	70 ± 6
Daytime SBP, mmHg	124 ± 5	ns	123 ± 5
Daytime DBP, mmHg	73 ± 6	ns	74 ± 6
Night-time SBP, mmHg	114 ± 11	ns	112 ± 10
Night-time DBP, mmHg	67 ± 7	ns	65 ± 9
24-h HR, beats/min	73 ± 7	ns	75 ± 9
LVDD, mm	46 ± 5	ns	45 ± 7
LVMI, g/m ²	84 ± 21	ns	89 ± 24
-dD/dt, s ⁻¹	3.5 ± 0.6	ns	3.7 ± 0.9
+dD/dt, s ⁻¹	5.9 ± 1.2	ns	5.7 ± 1.3
dW/dt, cm/s	13.6 ± 3.1	ns	13.2 ± 3.3
E/A	1.26 ± 0.13	ns	1.24 ± 0.15
E-DT, ms	172 ± 19	ns	168 ± 23

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVDD, LV end-diastolic diameter; LVMI, LV mass index; -dD/dt, peak shortening rate of LV diameter; +dD/dt, peak lengthening rate of LV diameter; dW/dt, peak thinning rate of LV posterior wall; E/A, ratio of peak E to peak A velocities; E-DT, deceleration time of E wave.

Table II. Clinical characteristics of the IO hypertensive patients who progressed to sustained hypertension (Group 1) and of those who did not (Group 2).

	Group 1 (n=25)			Group 2 (n=17)		
	Basal	p	2nd evaluation	Basal	p	2nd evaluation
Age, years	42 ± 6	<0.001	45 ± 5	43 ± 7	<0.001	46 ± 6
BMI, kg/m ²	25.8 ± 2.3	ns	25.6 ± 2.1	25.6 ± 2.1	ns	25.8 ± 2.4
Clinic SBP, mmHg	146 ± 8	ns	147 ± 7	148 ± 13 ^a	0.007	138.5 ± 10 ^b
Clinic DBP, mmHg	90 ± 7	<0.001	99 ± 8	91 ± 11	ns	88.5 ± 5 ^b
24-h SBP, mmHg	120 ± 4	<0.001	134 ± 6	119 ± 5	ns	120 ± 4 ^b
24-h DBP, mmHg	71 ± 4	<0.001	85 ± 8	70 ± 4	ns	72 ± 4 ^b
Day SBP, mmHg	124 ± 4	<0.001	139 ± 6	123 ± 4	ns	125 ± 4 ^b
Day DBP, mmHg	75 ± 5	<0.001	89 ± 8	75 ± 4	ns	76 ± 5 ^b
Night SBP, mmHg	113 ± 11	0.006	125 ± 9	110 ± 12	ns	113 ± 9 ^b
Night DBP, mmHg	69 ± 9	<0.001	77 ± 8	66 ± 8	ns	68 ± 9 ^b
24-h HR, beats/min	74 ± 9	ns	76 ± 7	74 ± 8	.02	71 ± 8 ^b

^ap < 0.02 Group 2 vs Group 1 at the basal evaluation. ^b0.05 < p < 0.001 Group 2 vs Group 1 after 3 years. Abbreviations as in Table I.

values unchanged compared with basal values (Table I).

Out of the 42 IO hypertensive patients who underwent the second evaluation, 17 subjects still had IO hypertension (office BP > 140 and/or 90 mmHg and daytime BP < 130/80 mmHg),

whereas 25 subjects had clinic BP > 140 and/or 90 mmHg and daytime BP > 135 and/or 85 mmHg. Considering these 25 patients together with the 19 patients not reevaluated because they have already developed sustained hypertension and were on antihypertensive treatment (see Methods section;

Figure 1), 44/61 patients with IO hypertension (72%) developed ambulatory hypertension over a 3-year period.

On the basis of these results, we divided the 42 patients evaluated into two groups: 25 patients who developed sustained hypertension (Group 1) and 17 patients with IO hypertension (Group 2).

Looking for possible markers of the subsequent development of sustained hypertension, we compared basal BP and LV characteristics of Groups 1 and 2. The two groups did not differ with regard to gender (men/women Group 1 11/14, Group 2 7/10, ns), age, body mass index and 24-h heart rate (Table II). Office systolic BP was higher in Group 2, whereas office diastolic BP and ambulatory systolic and diastolic BP throughout the 24 h were not significantly different between the two groups (Table II). Considering basal LV morpho-functional characteristics (Table III), LV end-diastolic diameter was normal (<56 mm) in all the patients and similar between the two groups; mean values of LV mass index (LVMI) were also similar between the two groups, whereas LV hypertrophy (LVMI ≥ 130 g/m² men, ≥ 110 g/m² women) was found in six patients, all in Group 1. LV systolic function was normal (peak shortening rate of LV diameter >1.9 s⁻¹) in all the patients and similar between the two groups. With regard to LV diastolic function, mean values of peak lengthening rate, peak thinning rate of LV posterior wall and E/A ratio were significantly lower and deceleration time of E wave longer in Group 1 than in Group 2; a preclinical LV diastolic impairment (two or more of the following: peak lengthening rate of LV diameter <3.6 s⁻¹, peak thinning rate of LV posterior wall <8.4 cm/s, E/A ratio <1) was found in 15 patients, all in Group 1. Therefore all the 16 patients with basal myocardial hypertrophy and/or preclinical diastolic dysfunction belonged to Group 1. Comparing the two groups of IO hypertensive patients with the normotensive

group, mean values of all LV morpho-functional characteristics were similar between normotensives and Group 2, whereas Group 1 showed significantly higher LV mass index and lower diastolic indices (Tables I and III).

The mean follow-up period was not significantly different between the groups (Group 1 3.4 ± 0.2 years, Group 2 3.4 ± 0.1 years, Normotensive group 3.4 ± 0.2 years, ANOVA ns).

Considering longitudinal changes within each group, after 3 years, body mass index was unchanged in the normotensive group, as well as in Group 1 and Group 2 (Tables I and II). All the 38 normotensive subjects had LV morpho-functional parameters within the normal limits and unchanged compared with basal values (Table I). In Group 1, office diastolic BP and 24-h BP were significantly increased, peak thinning rate of LV posterior wall and E/A ratio were significantly decreased and deceleration time of E wave increased (Tables II and III); LV hypertrophy was found in eight patients and preclinical diastolic dysfunction in 17 patients, raising the number of subjects with preclinical cardiac damage to 18 subjects.

In Group 2, compared with basal values, office systolic BP was significantly lower, whereas the other BP parameters were unchanged, as well as all LV parameters (Tables II and III); moreover all the patients had LV mass index and LV diastolic parameters within the normal limits, as at the basal evaluation.

Discussion

The prevalence of IO hypertension, as well as its association with target organ damage and incidence of cardiovascular events, differ markedly among the studies, not only because of differences in age, sex and body mass index of the subjects evaluated, but also depending on the threshold used to define

Table III. Left ventricular (LV) morpho-functional characteristics of IO hypertensive patients who progressed to sustained hypertension (Group 1) and of those who did not (Group 2).

	Group 1 (n=25)			Group 2 (n=17)		
	Basal	p	2nd evaluation	Basal	p	2nd evaluation
LVDD, mm	48 ± 4	ns	48 ± 5	47 ± 5	ns	48 ± 6
LVMI, g/m ²	97 ± 29 ^a	ns	103 ± 27	86 ± 21	ns	93 ± 24
-dD/dt, s ⁻¹	3.4 ± 0.9	ns	3.3 ± 0.7	3.6 ± 0.8	ns	3.5 ± 0.7
+dD/dt, s ⁻¹	4.5 ± 1.1 ^a	ns	4.3 ± 1.4	5.7 ± 1.7 ^c	ns	5.3 ± 1.2 ^c
dW/dt, cm/s	10 ± 2.7 ^a	0.008	8.9 ± 3.6	12.7 ± 2.3 ^c	ns	12.3 ± 2.6 ^c
E/A	1.08 ± 0.28 ^a	0.024	1.04 ± 0.25	1.23 ± 0.18 ^c	ns	1.17 ± 0.16
E-DT, ms	186 ± 33 ^a	0.005	210 ± 41	165 ± 22 ^c	ns	173 ± 31 ^c

^a0.05 $< p < 0.001$ Group 1 vs Normotensive group (Table I) at the basal evaluation. ^b0.05 $< p < 0.002$ Group 2 vs Group 1 at the basal evaluation. ^c $p < 0.005$ Group 2 vs Group 1 after 3 years. Abbreviations as in Table I.

normal daytime ambulatory BP (18,19). Obviously, choosing a high value (e.g. 140/90 mmHg) as upper normal limit of daytime BP can lead to classify as IO hypertensive subjects who actually have sustained hypertension (18,20,21). The most widely used criterion to define IO hypertension refers to a daytime BP < 135/85 mmHg (1,22). Aiming to evaluate long-term changes of BP and LV characteristics in patients with IO hypertension, we chose as upper normal limit for daytime BP the more restrictive value of 130/80 mmHg; as BP values below this limit are to be regarded as definitely normotensive (23), using this cut-off value we aimed to avoid the recruitment of sustained hypertensives as IO hypertensive subjects.

Growing interest has emerged in recent years about IO hypertensive subjects: they share a number of hemodynamic and metabolic characteristics with sustained hypertensives. Several studies (24,25) have shown that IO hypertension is associated with sympathetic hyperactivity, which not only could play a role in the evolution towards sustained hypertension, but could also contribute to the development of target organ damage. In fact, we can speculate, according to Smith et al. (25), that transient BP increases caused by exaggerated responses to mild stress, such as during medical evaluation, may influence myocellular growth, leading to cardiac hypertrophy and arterial wall thickening.

Today the natural history of patients with IO hypertension is still unclear. Bidlingmeyer and coworkers (13) found that, over a 5–6-year period, 60 IO hypertensives of 81 subjects (74%) developed sustained hypertension, but the results could have been influenced by the high daytime BP value considered as upper normal limit (140/90 mmHg) for the definition of IO hypertension. A lower rate of progression (37%) to sustained hypertension was found by Verdecchia and coworkers (14) over a period of between 6 months and 6.5 years (mean follow-up 2.5 years), using as upper normal limit of daytime BP 131/86 mmHg in women and 136/87 mmHg in men. Using a cut-off value of 132/84 mmHg for the daytime diastolic BP, during a 3.5-year follow-up, Polonia and coworkers (15) found a similar rate of progression to ambulatory hypertension in IO hypertensives (22%) and in normotensive subjects (15%). In our study, during a 3-year period, 72% of IO hypertensives developed sustained hypertension, a rate of progression higher than that found by Verdecchia et al. (14) and by Polonia et al. (15). Taking into account the lower cut-off value we used as upper normal limit of daytime BP (< 130/80 mmHg) and the shorter

follow-up period, the incidence of ambulatory hypertension in our IO hypertensives was also higher than Bidlingmeyer et al.'s (13). As an increase in body weight can induce *per se* an increase in BP (26), we have to underline that during the follow-up, body mass index did not change in all the patients. Over the same 3-year period, we evaluated a control group of normotensive subjects. At the basal evaluation, they were similar to IO hypertensive subjects with regard not only to age, gender and body mass index, but also to 24-h BP values; none of the 38 normotensive subjects developed sustained hypertension during the follow-up. Our control group was small, therefore we considered it useful to compare our results also with those from the Framingham study (27), which evaluated the progression to hypertension in a large cohort of normotensive subjects: in the age group 35–64 years, during a 3-year period, 13.5% of subjects with normal BP and 29.6% with high-normal BP progressed to hypertension. Therefore the incidence of sustained hypertension is significantly higher in our group of IO hypertensives (72%) than in normotensive subjects, in all the baseline BP categories. We do not have an explanation for the lack of progression to hypertension in our normotensive group; we can only underline two major differences in comparison with the Framingham study: the smaller number of subjects we evaluated and the normal BP that we established not only on the basis of office measurements, but also by means of 24-h ambulatory monitoring, a way to make more likely the recruitment of truly normotensive subjects.

The other aim of our study was to look for possible BP or LV characteristics at the basal evaluation that could predict the progression to sustained hypertension. At baseline, the group who became hypertensive and the group who did not were not significantly different, considering age, gender, body mass index, all ambulatory BP parameters and diastolic clinic BP; only clinic systolic BP was significantly higher, but in the group that did not become hypertensive. Therefore, the subsequent progression to sustained hypertension could not be predicted on the basis of clinic or ambulatory BP values, gender or body mass index.

Considering LV characteristics, at the basal evaluation preclinical cardiac damage (myocardial hypertrophy and/or diastolic dysfunction) was found in 16 patients with IO hypertension, whereas all the LV parameters were within the normal limits in the normotensive control group: this finding is in agreement with many (6,8,9), but not all the previous studies (2–4) that evaluated cardiac morphology and function in IO hypertension.

Comparing the two IO hypertensive groups, only mean values of diastolic parameters were significantly different with a pattern of preclinical diastolic impairment in the group who subsequently became hypertensive. Moreover, all 16 patients with myocardial hypertrophy and/or preclinical diastolic dysfunction belonged to the group that progressed to sustained hypertension.

The subjects who have not become sustained hypertensive had all LV parameters within the normal limits and similar to normotensive subjects, at the basal as well as at the 3-year evaluation, whereas the group that progressed to sustained hypertension showed at the 3-year evaluation a significant worsening of LV diastolic indices.

LV diastolic function is a complex phenomenon that can not be characterized by a single non-invasive parameter, therefore, in order to better evaluate the diastole, we used two methods (digitized M-mode echo and Doppler evaluation of transmitral flow) that explore different aspects of LV diastolic function (28,29): Doppler indices measure peak velocities of flow, whereas the parameter derived from digitized M-mode echo measures changes in dimension. These diastolic parameters, less popular than Doppler-derived indices, have been proved very sensitive in discriminating between normal and abnormal diastole and are far less influenced by age and heart rate than Doppler indices (29).

In conclusion, our results indicate that subjects with IO hypertension are at increased risk of developing sustained hypertension, also when IO hypertension is defined by means of a daytime BP threshold more restrictive than those employed in previous studies. Moreover, beside confirming the presence of cardiac damage in IO hypertension, this study shows that the progression towards sustained hypertension cannot be predicted on the basis of gender, body mass index, clinic or 24-h ambulatory BP values, whereas the presence of a preclinical cardiac damage seems to be the only characteristic that predicts the subsequent development of sustained hypertension. In fact, all subjects with basal myocardial hypertrophy and/or preclinical diastolic dysfunction became sustained hypertensive. Therefore, all the subjects with IO hypertension should be controlled over time and also counseled about lifestyle modifications in order to reduce the risk of progression towards hypertension; the lifestyle counseling, together with an adequate drug treatment, are mandatory for patients with IO hypertension and preclinical cardiac damage, this latter defining a condition of high cardiovascular risk.

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