Persistence of increased left ventricular mass despite optimal blood pressure control in hypertension

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Echocardiography; Hypertension, arterial; Hypertrophy; Treatment.

Background. **Left ventricular hypertrophy is an adverse risk marker in essential hypertension and its regression has a favorable effect on prognosis. It is unclear whether blood pressure normalization induced by long-term therapy is able to normalize left ventricular mass completely.**

Methods. **In the setting of a prospective cohort study, 107 consecutive hypertensive patients who achieved blood pressure normalization (clinic blood pressure < 140/90 mmHg on Ž 3 consecutive visits) under long-term (1-10 years, average 2.9) drug treatment were individually matched with 107 healthy normotensive controls by gender, age (± 5 years), body mass index (± 3 kg/m^2), and clinic systolic blood pressure (± 5 mmHg) in a case-control design. All subjects underwent 24-hour blood pressure monitoring and M-mode echocardiography.**

Results. **Treated hypertensive patients and normotensive controls did not differ by age, body mass index, clinic blood pressure (128/82 vs 128/81 mmHg), and 24-hour blood pressure (120/77 vs 120/76 mmHg). Left ventricular mass and relative wall thickness were greater in the hypertensive than in the normotensive group (97 ± 24 vs 86 ± 17 g/m^2 and 0.40 ± 0.08 vs 0.37 ± 0.08, both p < 0.001).**

Conclusions. **Left ventricular mass is greater in well-controlled hypertensive patients than in normotensive controls matched by age, obesity, gender, and clinic and 24-hour blood pressure. This finding is consistent with the lower than epidemiologically expected reduction in coronary heart disease risk during antihypertensive therapy and might reflect the persistent effect on left ventricular mass of hemodynamic and/or non-hemodynamic factors other than blood pressure in treated patients with essential hypertension.**

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Introduction

Left ventricular (LV) hypertrophy detectable on echocardiography is a powerful independent risk marker for cardiovascular complications and death in essential hypertension[1-3], and its regression predicts a better outcome regardless of the treatment-induced reduction in blood pressure (BP)[4,5].

Randomized controlled trials of drug treatment in hypertension have shown that long-term antihypertensive treatment leads to a reduction in coronary events, but the observed benefit is significantly lower than one would expect from observational studies, whereas the observed reduction in stroke incidence is similar in size to the epidemiologically expected benefit[6,7]. A possible explanation for this finding might be the persistence of a greater LV mass in treated hypertensive patients, despite normalization of BP. The present case-control study was designed to investigate whether BP normalization induced by long-term antihypertensive treatment is associated with regression of LV mass to fully normal values. We determined LV mass at echocardiography in a group of treated hypertensive patients with normal in-treatment BP, and compared them with a group of normotensive subjects matched by age, gender, BP, and body mass index in a case-control design.

Methods

The present study is an analysis of 107 patients with essential hypertension, consecutively drawn from a larger group of 689 white hypertensive subjects (mean age 51 ± 12 years)[3,8,9], and compared with 107 healthy normotensive subjects. All subjects were

included in the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, a prospective observational registry of morbidity and mortality carried out in patients with essential hypertension and in a control group of normotensive subjects, whose initial diagnostic work-up included 24-hour non-invasive ambulatory BP monitoring and echocardiography according to a standardized protocol[3,9]. Hypertensive patients were referred to one of three participating centers (Perugia, Città della Pieve and Castiglione del Lago, Italy) for baseline evaluation by a group of general practitioners practising in Umbria, in central Italy, and fulfilled all the following criteria: 1) clinic systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or both on ≥ 3 visits at 1-week intervals; 2) no previous treatment for hypertension, or withdrawal from antihypertensive drugs ≥ 4 weeks before the study; 3) no clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects or secondary causes of hypertension, or important concomitant disease; 4) good-quality echocardiographic recordings; 5) ≥ 1 valid BP measurement per hour over the 24 hours. Normotensive subjects were members of the hospital staff or subjects examined for clinical check-up and found healthy. All had clinic systolic BP < 140 mmHg and diastolic BP < 90 mmHg on ≥ 3 occasions, and fulfilled the above points 3) to 5). In the PIUMA study, all subjects are followed by their family physicians, in cooperation with the outpatient clinic of the referring hospital, and treated with the aim of reducing clinic BP to < 140/90 mmHg by the use of pharmacological measures and a standard lifestyle. Most patients continue to be periodically referred to our institutions for BP control and other diagnostic procedures. All subjects gave informed consent to the study.

Identification of case and control subjects. In the setting of the PIUMA study, 689 patients with essential hypertension who had undergone baseline off-treatment 24-hour BP monitoring and M-mode echocardiography repeated both investigations under antihypertensive drug treatment after an average follow-up of 3.1 years. From these patients we excluded all subjects with: 1) diabetes mellitus (fasting glucose > 7.8 mmol/l, or hypoglycemic therapy; n = 61); 2) prior antihypertensive drug treatment at the baseline examination (n = 211); 3) suboptimal echocardiographic study at the follow-up examination (n = 23); 4) incomplete in-treatment clinic BP normalization (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, n = 199); and 5) interruption of drug therapy for > 2 weeks during the treatment period (n = 88). Thus, 107 patients satisfied all the following criteria: 1) no previous or current antihypertensive treatment at the first 24-hour BP monitoring and echocardiographic study; 2) uninterrupted antihypertensive drug therapy for ≥ 1 year during subsequent follow-up; 3) repeated in-treatment good-quality 24-hour BP monitoring and echocardiographic study; 4) complete BP normalization during drug therapy (clinic systolic BP < 140 mmHg and diastolic BP < 90 mmHg on each of ≥ 3 visits in the month preceding the in-treatment ambulatory BP monitoring); and 5) no diabetes mellitus. After erasing from the working copy of the computer file all the BP and echocardiographic data, hypertensive patients were individually matched with 107 healthy normotensive subjects by age (within 5 years), gender (same gender), clinic systolic BP (within 5 mmHg) and body mass index (within 3 kg/m^2). Several different drug classes were used for BP control in hypertensive patients. Fifty-three patients (49%) were treated with one drug, and 54 (51%) with a combination of drugs. The most commonly used drugs were angiotensin-converting enzyme inhibitors (62%), diuretics (44%), Ca^{2+}-channel blockers (34%), and β-blockers (18%).

Blood pressure measurement. Clinic BP was measured by a physician in the hospital outpatient clinic with a mercury sphygmomanometer, with the subject sitting for ≥ 10 min. The average of 6 measurements on ≥ 2 sessions was considered for the analysis. Ambulatory BP was recorded using an oscillometric device (models 90202 and 90207, SpaceLabs, Redmond, WA, USA), set to take a reading every 15 min throughout the 24 hours. Normal daily activities were allowed and encouraged, and patients were told to keep their non-dominant arm still and relaxed to the side during measurements. The day of ambulatory BP monitoring, hypertensive patients had drug therapy in the outpatient clinic, immediately before starting BP monitoring. In order to abide by the actual wakefulness-sleep rhythm, day and night were defined according to patients' diaries. Nighttime workers were excluded from the present study. Reading, editing and analysis of data were done as previously reported[9].

Echocardiography. The M-mode echocardiographic study of the left ventricle was performed under two-dimensional control. Measurements were taken according to the American Society of Echocardiography recommendations[10]. Only frames with optimal visualization of interfaces and showing simultaneously septum, LV internal diameter and posterior wall were used for reading. Tracings were read by two observers who were unaware of patients' clinical data, and the mean value from ≥ 5 measurements per observer was computed. The intraobserver and intratracing variabilities in our laboratory have been reported elsewhere[11]. LV mass was calculated according to Devereux et al.[12], and normalized by both body surface area and height$^{2.7}$ [13], to correct the effect of overweight. Relative wall thickness was calculated as (2 X posterior wall thickness/LV internal diameter). LV mechanics was assessed at both the chamber level (as endocardial fractional shortening) and the midwall level, according to a geometric model that takes into account the non-uniform systolic thickening of the LV wall[14]. Fractional shortening was considered in both absolute terms and after correction for afterload, as a per-

centage of the predicted value on the basis of the regression equation between end-systolic circumferential wall stress[15] and fractional shortening in a group of 130 normotensive subjects (66 men, 64 women, 44 ± 13 years, clinic BP 126/79 ± 8/6 mmHg). The two-dimensional study showed a symmetrical LV contraction in all subjects and thus LV volumes were calculated with the use of the Teichholz formula[16]; this method has recently been shown to estimate accurately LV volumes in nondilated left ventricles and to parallel closely Doppler-derived stroke volume in a large population sample[17]. Stroke work, a measure of cardiac workload, was calculated as systolic BP times stroke volume, and converted into gram-meters by multiplying it by 0.0144[18]. Pulsed Doppler interrogation of LV inflow tract was performed from the apical 4-chamber view with the sample volume positioned at the level of the tips of mitral valve leaflets, as previously described[19]. Peak E and peak A velocities and their ratio were the average of ≥ 10 cardiac cycles.

Statistical analysis. Normotensive and hypertensive groups were compared by Student's t test for paired samples and χ^2 test when appropriate. Hypertensive patients were divided into three groups according to treatment duration (from 1 to 2 years, from 2 to 3 years, and from 3 to 10 years), and the groups were compared through the use of one-way analysis of variance and Tukey's post-hoc test for multiple comparisons. The relation between treatment duration and LV mass reduction was assessed through the use of Pearson's correlation coefficients. A p value of < 0.05 was considered statistically significant. Data are presented as mean ± SD.

Results

The average duration of antihypertensive treatment in the study subjects was 2.9 years (range 1-10 years). Some demographic and clinical characteristics of the study population are reported in table I. By matching, age, gender, body mass index and clinic BP were virtually identical in normotensive and hypertensive subjects. Drinking and smoking habits, body surface area, and lipid profile did not differ. Average 24-hour BP, awake BP and asleep BP were similar in the study groups. Normotensive subjects had a slightly higher heart rate as measured by the physician ($p < 0.003$), but not within the 24 hours.

As shown in table II, LV mass was significantly higher in the hypertensive than in the normotensive group, after indexation by both height$^{2.7}$ ($p < 0.0005$) and body surface area ($p < 0.0001$). Hypertensive patients showed a more concentric LV geometry ($p < 0.0003$ for relative wall thickness), resulting from a persistent increase in septum and posterior wall thickness, without any significant differences in LV internal dimension. Twenty-four-hour BP monitoring and echocardiography had also been performed in hypertensive patients at the baseline visit, before starting drug treatment. Both clinic (155/100 ± 16/9 mmHg) and 24-hour (140/90 ± 13/10 mmHg,) pre-treatment BP values were normalized by treatment, with a reduction of 17/18% (clinic BP) and 14/14% (24-hour BP) compared to pre-treatment values. These changes were accompanied by a 14% reduction in LV mass (from 51.4 ± 15 to 44.3 ± 11 g/m$^{2.7}$, $p < 0.0001$), and by a 9% reduction in relative wall thickness (from 0.44 ± 0.09 to 0.40 ± 0.08, $p < 0.0001$). The proportion of hypertensive patients with clear-cut LV hypertrophy (LV mass index Ž 50 g/m$^{2.7}$ in men or Ž 47 g/m$^{2.7}$ in women) was 48% before treatment, and decreased to 28% after treatment ($p < 0.01$). However, the prevalence of LV hypertrophy in hypertensive patients under drug treatment was still significantly higher than in the normotensive group (10%, $p < 0.002$).

LV systolic performance was lower in treated hy-

Table I. Demographic and clinical characteristics of subjects.

Data	Normotensive subjects (n=107)	Hypertensive subjects (n=107)	p
Age (years)	50.1 ± 10	51.1 ± 10	0.44
Men/women	64/43	64/43	1.00
Body mass index (kg/m^2)	26.8 ± 3	26.4 ± 3	0.40
Body surface area (m^2)	1.86 ± 0.2	1.84 ± 0.2	0.47
Alcohol intake (g/day)	21 ± 30	19 ± 30	0.52
Current smokers (%)	29	24	0.41
Total cholesterol (mmol/l)	5.61 ± 1.1	5.64 ± 1.2	0.88
HDL cholesterol (mmol/l)	1.26 ± 0.4	1.31 ± 0.3	0.42
Triglycerides (mmol/l)	1.61 ± 0.8	1.52 ± 0.9	0.52
Clinic SBP/DBP (mmHg)	128/81 ± 8/7	128/82 ± 7/6	0.66/0.16
24-hour SBP/DBP (mmHg)	120/76 ± 9/7	120/77 ± 8/6	0.60/0.67
Awake SBP/DBP (mmHg)	124/80 ± 9/7	125/81 ± 8/6	0.36/0.20
Asleep SBP/DBP (mmHg)	111/68 ± 10/8	112/68 ± 9/7	0.61/0.99
Clinic heart rate (b/min)	74 ± 8	71 ± 9	< 0.003
24-hour heart rate (b/min)	74 ± 7	73 ± 9	0.46

Data are expressed as mean ± SD. DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table II. Echocardiographic characteristics of subjects.

Data	Normotensive subjects (n=107)	Hypertensive subjects (n=107)	p
Interventricular septum (mm)	9.5 ± 2	10.7 ± 2	< 0.0001
Posterior wall (mm)	8.8 ± 2	9.6 ± 2	< 0.0005
LV internal dimension (mm)	49.6 ± 5	48.5 ± 5	0.12
LV mass/BSA (g/m^2)	86.2 ± 17	97.2 ± 24	< 0.0001
LV mass/height$^{2.7}$ ($g/m^{2.7}$)	39.4 ± 9	44.3 ± 11	< 0.0005
Relative wall thickness	0.37 ± 0.08	0.40 ± 0.08	< 0.0003
Circumferential wall stress (g/cm^2)	116.2 ± 33	106.9 ± 33	< 0.04
FS (%)	38.4 ± 7	39.1 ± 7	0.45
Afterload-corrected FS (%)	101.2 ± 11	99.0 ± 13	0.17
Midwall FS (%)	18.4 ± 3	17.0 ± 3	< 0.0004
Afterload-corrected midwall FS (%)	100.7 ± 16	91.5 ± 15	< 0.0001
Stroke work (gum/beat)	143.4 ± 40	140.3 ± 37	0.56
Mitral E/A wave velocity ratio	1.15 ± 0.31	1.12 ± 0.37	0.57

Data are expressed as mean ± SD. BSA = body surface area; FS = fractional shortening; LV = left ventricular.

pertensives than in normotensives when measured at the midwall level, both in absolute terms ($p < 0.0004$, Table II) and after adjustment for end-systolic stress ($p < 0.0001$). In hypertensive patients, midwall shortening fraction increased by 8% after treatment compared with pre-treatment values (from 15.7 ± 3 to 17.0 ± 3%, $p < 0.0001$), although remaining significantly lower than in the normotensive group. In contrast, no difference was found between hypertensive and normotensive subjects when LV shortening fraction was measured at the endocardial level ($p = 0.45$). Stroke work decreased during treatment (from 163.5 ± 36 to 140.3 ± 37 gum/beat, $p < 0.001$), and the achieved values were comparable with those of normal subjects ($p = 0.56$, Table II). The ratio between early and atrial LV inflow velocities in hypertensive patients increased with treatment (from 1.04 ± 0.36 to 1.12 ± 0.37, $p < 0.04$), and the achieved values did not differ from those of normotensive subjects ($p = 0.57$, Table II).

To evaluate the possible influence of the duration of treatment on LV mass changes, hypertensive subjects were divided into three groups on the basis of the duration of drug treatment: from 1 to 2 years (n = 38), from 2 to 3 years (n = 31), and from 3 to 10 years (n = 38). No differences were found between the three groups in terms of percent change in LV mass compared to pre-treatment values (-14 ± 14, -14 ± 12, and -12 ± 14%, respectively; $p = 0.28$), and in 24-hour systolic BP change (-14 ± 7, -12 ± 8, and -14 ± 8 mmHg; $p = 0.52$). As depicted in figure 1, no significant association was found between the degree of treatment-induced LV mass change and the duration of treatment ($r = 0.09$, $p = NS$).

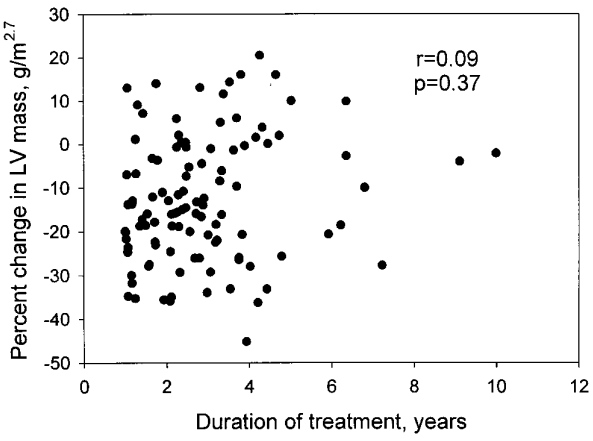

Figure 1. *The scatter plot shows the absence of a significant relation between percent left ventricular (LV) mass reduction (in-treatment minus pre-treatment values) and the duration of drug treatment.*

Discussion

The main finding of this study is that patients with essential hypertension under long-term antihypertensive treatment, and whose clinic and 24-hour BP was fully normalized after an average 3-year treatment, showed a greater LV mass, a more concentric LV geometric pattern and a decreased afterload-corrected midwall systolic function when compared with normotensive controls. Hypertensive and normotensive subjects were accurately matched by age, gender, body mass index, and clinic and 24-hour BP in a case-control design. The achieved values of LV mass, relative wall thickness and midwall fractional shortening were intermediate between pre-treatment values and the values observed in age- and BP-matched normotensive subjects.

It is generally established that pressure overload is only one determinant of LV mass in essential hypertension, along with body size, gender, obesity, age, exercise, smoking, alcohol intake, high sodium intake, and several genetic factors[20]. The correlation between BP and LV mass is generally weak in hypertensive patients, and also 24-hour BP – which is generally considered more representative of an individual's usual BP than the average of a few office measurements – usually accounts

for no more than 25% of the overall variance of LV mass[21]. Increased LV mass is not only an adaptation to increased afterload, but also a predictor of future development of clinically evident arterial hypertension in normotensive subjects[22-25]. Several experimental studies suggest the role of non-hemodynamic mediators of LV hypertrophy, including angiotensin II[26,27], catecholamines[28,29], and genetic susceptibility[30]. Our finding of a greater LV mass in treated hypertensive patients than in normotensive subjects with similar BP and stroke work values suggests that the increased LV mass in this setting appears to be partially dependent upon workload-independent mechanisms, which may continue to work even during drug treatment, despite complete long-term BP normalization. Another possibility to consider is the development of irreversible cardiac structural changes in hypertensive patients[31], with a consequently difficult achievement of complete normalization of LV mass. In animal studies, treatment with angiotensin-converting enzyme inhibitors is effective in preventing fibrosis[32], but not in reversing fibrosis once it is well established[33].

The persisting abnormalities of LV mass and geometry in patients with optimally controlled BP are consistent with the finding that, in randomized trials of drug treatment in hypertension, the observed 16% reduction in coronary events associated with a relatively prolonged 5-6 mmHg lowering in usual diastolic BP is only about two thirds of the full effect (estimated as 21-25%) to be expected from observational studies for a corresponding BP difference. In contrast, the 38% stroke reduction observed in randomized trials is similar in size to the 35-40% expected from observational studies[6,7]. Our data provide one possible insight into this inconsistency, by showing that LV mass, a strong independent risk marker for coronary heart disease, remains greater by approximately 13% in the hypertensive patients, despite their full BP control, than in matched normotensive subjects. Such a difference could be predictive of increased risk, given the linear relation between LV mass and cardiovascular risk[34]. As a matter of fact, a significant relation between LV mass and cardiovascular risk is already detectable at LV mass values (> 105 g/m^2 in men, > 91 g/m^2 in women) well below the current upper normal limits[34].

One potential explanation for our findings is that the duration of treatment (2.9 years on average in the present study) was not long enough to achieve a complete normalization of LV mass. This possibility is supported by a recent study performed in 26 hypertensive patients with LV hypertrophy treated over a 3-year period with an angiotensin-converting enzyme inhibitor[35]. In that study, LV mass decreased further after the first 6 months up to 3 years. In our study, however, patients were treated for up to 10 years and the average reduction in LV mass induced by treatment was comparable in the groups with different duration of antihypertensive treatment. In addition, no significant relation was found between the degree of treatment-induced LV mass change and the duration of treatment.

A second possibility is that the structural abnormalities described in pressure overload LV hypertrophy might become permanent after a long time of exposition to the abnormal overload[36]. This possibility is supported by the evidence that, while gender, body size and cardiac workload as stroke work explain up to 82% of the normal variance of LV mass[18], a "compensatory" increase in LV mass cannot be found in all hypertensive patients, LV mass being inappropriately high in about one third of subjects with essential hypertension with poorer outcome[37].

A third explanation for our finding might be that baseline, pre-hypertensive LV mass might be higher in subjects with future development of hypertension than in subjects who will not develop hypertension[22-24]. In this case, antihypertensive treatment could have indeed determined a full regression of LV hypertrophy to these "baseline" levels. The cross-sectional, case-control design of our study does not allow us to rule out this possibility.

In our study, LV inflow velocity pattern in treated hypertensives was not dissimilar from that in normotensives, in contrast with the persisting increase in LV mass. This finding is in agreement with the observation that LV mass has only a limited degree of association with diastolic function parameters[19,38,39], and lends support to the view that LV hypertrophy and LV diastolic dysfunction may have partially different determinants in essential hypertension.

The present study has some limitations. First, the assessment of drug compliance was based upon the patient's self-report, and ambulatory BP monitoring was performed only twice – once before treatment, and once at the end of the follow-up period. In the absence of serial ambulatory BP determinations during follow-up, we have limited information on the degree of long-term 24-hour BP control in the study subjects. Nevertheless, all the subjects who had discontinued drug therapy for Ž 2 weeks during the treatment period were excluded from the study. Secondly, several different classes of drugs were used for BP control, and thus our conclusions may not be necessarily applied to particular drug classes or combinations. It is worth noting that the distribution of antihypertensive drug classes in our study closely matches that of another large Italian hypertensive population[40]. The size and design of our study do not allow us to exclude the existence of clinically relevant differences among the various drug classes and combinations. A recent meta-analysis of the available controlled trials suggests that angiotensin-converting enzyme inhibitors and Ca^{2+}-channel blockers may be more effective than other drugs in determining LV hypertrophy regression[41], but other clinical trials with head-to-head comparison failed to confirm this finding[42-44], which would be an important question to be addressed in future, specifically designed trials.

To sum up, patients with essential hypertension under long-term therapy showed persistently elevated LV mass and concentric geometric pattern despite optimal control of their clinic and ambulatory BP. These changes were independent of age, gender, obesity, and other confounding factors. These data may reflect the persistent effect of trophic factors on LV mass in these patients, and/or the presence of irreversible cardiac structural abnormalities, and might contribute to explain the higher than expected incidence of coronary heart disease in treated patients with essential hypertension.

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