

ORIGINAL ARTICLE

Does the reduction in systolic blood pressure alone explain the regression of left ventricular hypertrophy?

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Systolic blood pressure (SBP) is an important determinant of the development and regression of left ventricular hypertrophy (LVH) in hypertensive humans. However, comparative assessments with other BP components are scarce and generally limited in size. As part of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA), 743 hypertensive subjects underwent echocardiography and 24-h ambulatory BP monitoring before and after an average of 3.9 years of treatment. The changes in left ventricular mass showed a significant direct association with the changes in 24-h SBP ($r=0.40$), diastolic blood pressure (DBP) ($r=0.33$) and pulse pressure (PP) ($r=0.35$). Weaker associations were found with the changes in clinic BP ($r=0.32$, 0.31

and 0.16 , respectively). In a multivariate linear regression analysis, the changes in 24-h SBP were the sole independent determinants of the changes in left ventricular mass (LVM) according to the following equation: percentage changes in LVM = $0.73 \times$ (percentage changes in 24-h SBP) -0.48 ($P<0.0001$). For any given reduction in 24-h SBP, the reduction in LVM did not show any association with the changes in DBP and PP, either clinic or ambulatory. These data indicate that SBP is the principal determinant of LVH regression in hypertensive humans.

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Introduction

Left ventricular mass (LVM) is a potent and independent marker of cardiovascular risk in a variety of clinical conditions including essential hypertension.^{1,2} Systolic blood pressure (SBP) and diastolic blood pressure (DBP) are important determinants of LVM. It is generally believed that the closeness of the association with LVM is generally greater with SBP than it is with DBP.^{2,3} Pulse pressure (PP), a marker of the stiffness of large arteries,⁴ has recently emerged as an important risk marker, and several studies have documented an association between increased PP and left ventricular hypertrophy (LVH).^{5–7}

Although the pathogenesis of LVH in hypertensive humans is quite complex due to the concurrent contribution of several haemodynamic and nonhae-

modynamic factors,² it is still uncertain which of the different BP components exerts the prevalent influence on the pathogenesis of LVH and its regression in hypertensive humans.

In a previous analysis of the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, a prospective registry of morbidity and mortality in initially untreated hypertensive subjects, after adjustment for the confounding effect of several covariates, the proportion of variability of LVM explained by SBP was greater than that explained by other BP components.⁸

As far as regression of LVH is concerned, the reduction in LVM during antihypertensive treatment is associated more closely with the reduction in 24-h ambulatory BP than with that of clinic BP,⁹ probably because 24-h ambulatory BP better reflects the BP overload to which the left ventricle (LV) is chronically subjected.¹⁰

In the present analysis of the PIUMA study, we assessed the associations between the serial changes in LVM and those of the various BP components in a large sample of hypertensive subjects who underwent echocardiography and 24-h ambulatory BP

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monitoring before and during sustained antihypertensive treatment.

Methods

Subjects

We studied 743 hypertensive subjects (56.0% men), mean age 47.6 years (s.d. 11), who attended the baseline visit and a follow-up visit in the setting of the PIUMA study. Details of the PIUMA registry have been reported previously.^{11,12} At entry, all patients had clinic SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg on at least three visits at 1-week intervals. All fulfilled the following inclusion criteria: (1) no previous treatment for hypertension or withdrawal from antihypertensive drugs at least 4 weeks prior to the study; (2) no clinic or laboratory evidence of heart failure, renal failure, coronary artery disease, valvular defects or secondary causes of hypertension; (3) at least one valid BP measurement per hour over the 24 h.

BP measurement

Clinic BP was measured using a standard mercury sphygmomanometer with the subject sitting for ≥ 10 min. Clinic heart rate was determined immediately thereafter. Caffeine ingestion and cigarette smoking were not allowed during the previous 2 h. Ambulatory BP was recorded using the SpaceLabs units 90202 and 90207 (SpaceLabs, Redmond, WA, USA) set to take a reading every 15 min throughout the 24 h. Normal daily activities were permitted, and patients were told to keep their nondominant arm still and relaxed at the side during measurements. The spontaneous day-to-day variability of ambulatory BP was assessed in some of these patients.¹³

Echocardiography

The M-mode echocardiographic study of the LV was performed under cross-sectional control using commercially available machines. At the time of the echocardiographic examination, all involved investigators were unaware of all patients' clinical data including office BP, ambulatory BP, and cardiovascular complications. LVM was determined using the formula introduced by Devereux *et al*:¹⁴ $0.80 \times \{1.04 \times [(\text{septal thickness} + \text{LV internal diameter} + \text{posterior wall thickness})^3 - (\text{LV internal diameter})^3]\} + 0.6$ g. In our laboratory,¹² the intraobserver coefficient of variation is 4.50% for septal thickness, 1.65% for LV internal diameter, 4.81% for posterior wall thickness and 6.33% for LVM index. The interobserver coefficient of variation is 6.30% for septal thickness, 1.65% for LV internal diameter, 6.73% for posterior wall thickness and 7.65% for LVM index.

Electrocardiography

Standard 12-lead ECGs were recorded in all subjects at 25 mm/s and 1 mV/cm calibration. Tracings were coded and interpreted by two investigators without the knowledge of other patient data. Interobserver differences occurred in less than 5% of readings and were resolved by consensus. Complete bundle branch block and Wolff-Parkinson-White syndrome were exclusion criteria from ECG analysis for LVH. Previous myocardial infarction and atrial fibrillation were exclusion criteria from the study. None of the subjects was being treated with digitalis. LVH was diagnosed by the Cornell/strain [C/S] index, a simple ECG index developed in our laboratory¹⁵ defined by the presence of either a classic strain pattern or a Cornell voltage (sum of R in aVL + S in V₃) > 2.0 mV in women or 2.4 mV in men, or both.

Follow-up

All subjects were followed by their family doctors in cooperation with the outpatient clinic of the referring hospital, and treated with the aim of reducing clinic BP below 140/90 mmHg using standard lifestyle and pharmacological measures. Therapeutic strategies were based upon clinic BP, although ambulatory BP reports remained accessible to patients and their doctors. Diuretics, β -blockers, ACE inhibitors, calcium channel blockers and α_1 -blockers, alone or in various combinations, were the antihypertensive drugs more frequently used.

The follow-up visit, including standard laboratory tests, 12-lead ECG, 24-h ambulatory BP monitoring, and echocardiography was undertaken after an average of 3.9 years of follow-up (s.d. 2.6). The protocol for experimental procedures was the same as in the baseline studies. None of the patients had developed a cardiovascular morbid event at the time of the follow-up visit.

Results

Tables 1 and 2 show the main characteristics of the study population at baseline and follow-up visit. The correlations between the changes in LVM and the changes in BP and anthropometric measures are summarized in Figure 1 and Table 3. The changes in LVM showed a closer association with the changes in average 24-h ambulatory BP ($r=0.40$ SBP and 0.33 DBP, both $P<0.001$) than with those in clinic BP ($r=0.32$ SBP and 0.32 DBP, both $P<0.001$) (Figure 2). The associations between the changes in LVM and the changes in clinic BP were generally weaker ($r=0.32$ with SBP, $r=0.31$ with DBP and $r=0.16$ with PP, respectively). There was a clinically consistent and statistically significant reduction in BP and LV mass over the follow-up period. The reduction in LVM was accounted for by a reduction in septum thickness ($P<0.001$) and

Table 1 Main demographic and clinical characteristics

Characteristic	
Number of subjects	743
Sex distribution (women/men)	328/415
Age (years)	48 ± 11
Weight (kg)	75.2 ± 14
Height (cm)	168.3 ± 9
Body mass index (kg/m ²)	26.4 ± 3.6
Known duration of hypertension (years)	3.9 ± 5.6

Data expressed as mean (±s.d.).

Table 2 Office and ambulatory BP and heart rate and echocardiographic characteristics before and during treatment

Characteristic	Baseline	Follow-up	P-value
Office SBP (mmHg)	155 ± 18	143 ± 17	<0.01
Office DBP (mmHg)	98 ± 9	90 ± 10	<0.01
Office heart rate (bpm)	75 ± 10	73 ± 11	<0.01
Average 24-h SBP (mmHg)	137 ± 14	128 ± 12	<0.01
Average 24-h DBP (mmHg)	87 ± 10	81 ± 8	<0.01
Average 24-h heart rate (bpm)	75 ± 9	73 ± 9	<0.01
Interventricular septum thickness (cm)	1.13 ± 0.2	1.04 ± 0.2	<0.01
LV internal diameter (cm)	4.94 ± 0.5	4.96 ± 0.5	NS
Posterior wall thickness (cm)	1.00 ± 0.2	0.97 ± 0.2	<0.01
LVM (g)	200 ± 63	186 ± 56	<0.01
LVM/height ^{2.7} (g/m ^{2.7})	48.8 ± 13.8	45.4 ± 12.0	<0.01
Total cholesterol (IU/l)	5.55 ± 1.07	5.70 ± 1.22	<0.01
HDL cholesterol (IU/l)	1.27 ± 0.32	1.35 ± 0.55	<0.01
LDL cholesterol (IU/l)	3.56 ± 0.92	3.60 ± 0.96	<0.01
Triglycerides (IU/l)	1.62 ± 1.10	1.67 ± 1.15	<0.05
Creatinine (IU/l)	86.2 ± 17	87.9 ± 30	NS
Glucose (IU/l)	5.49 ± 1.0	5.69 ± 1.7	<0.01

Data expressed as mean (±s.d.).

bpm, beats per minute; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

posterior wall thickness ($P < 0.001$), while the LV internal diameter remained virtually unchanged. There was also a small, albeit significant, increase in body weight from 75.1 to 76.0 kg ($P < 0.01$).

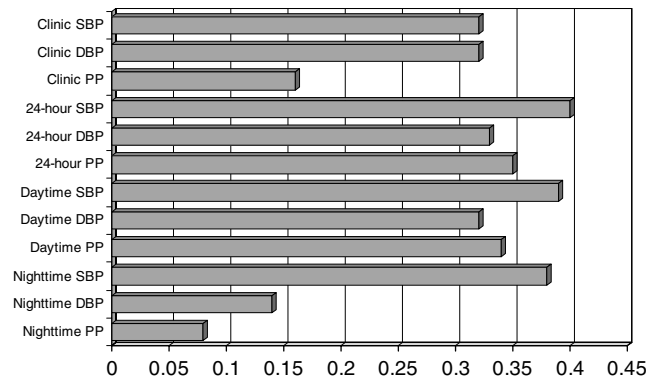


Figure 1 Correlation between the changes in LVM and the changes in the different BP components. PP, pulse pressure.

Table 3 Univariate relationships of the changes in LVM to the changes in BP and anthropometric measures

	Changes in LV mass	P-value
<i>Changes from baseline to treatment in</i>		
Office SBP	0.32	<0.01
Office DBP	0.32	<0.01
Office PP	0.16	<0.01
Average 24-h SBP	0.40	<0.01
Average 24-h DBP	0.33	<0.01
Average 24-h PP	0.35	<0.01
Average daytime SBP	0.39	<0.01
Average daytime DBP	0.32	<0.01
Average daytime PP	0.34	<0.01
Average nighttime SBP	0.38	<0.01
Average nighttime DBP	0.14	<0.01
Average nighttime PP	0.08	<0.05
Body weight	0.04	NS
Body mass index	0.01	NS

NS, nonsignificant.

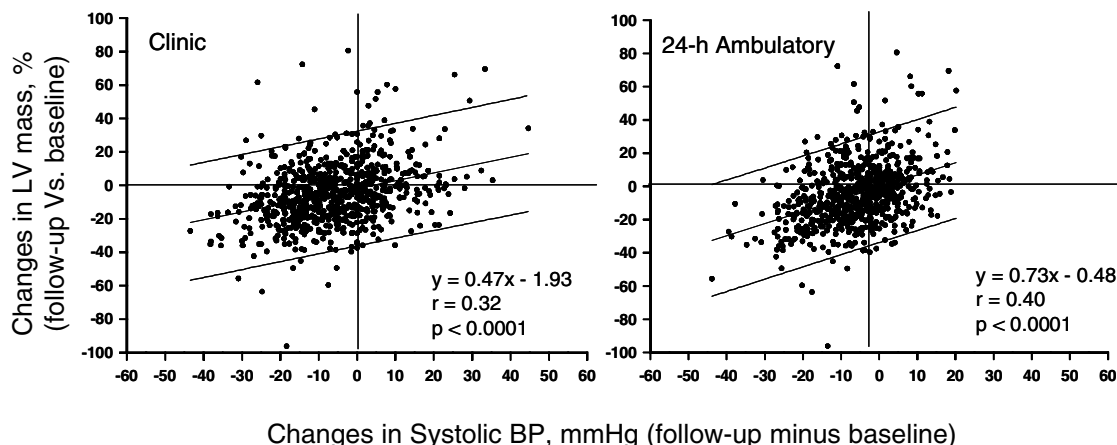


Figure 2 Association between the changes in left ventricular (LV) mass and the changes in clinic and ambulatory SBP.

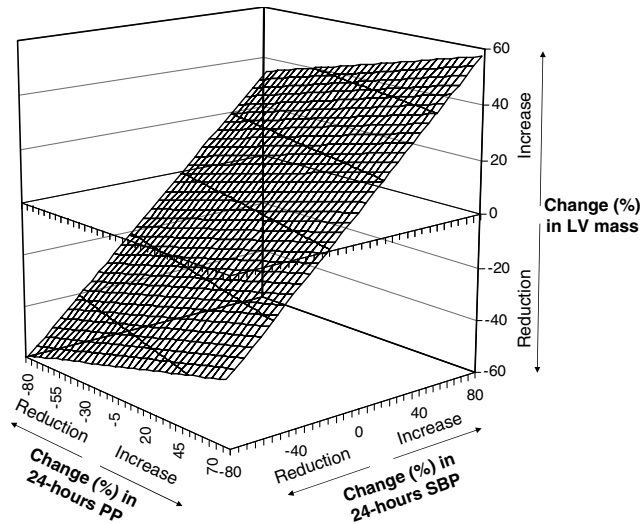


Figure 3 Relationship between the changes in left ventricular (LV) mass and the changes in ambulatory SBP and PP. The relationship was steeper with the changes in SBP than with those in PP.

Among the routine laboratory tests there was a small although statistically significant increase in total and high-density lipoprotein (HDL) cholesterol, and a nonsignificant increase in serum creatinine. The proportion of subjects receiving lifestyle measures only, diuretic, and/or β -blockers alone or combined, ACE inhibitors and/or calcium channel blockers alone or combined, or various drug associations was 31, 11, 18, and 41%, respectively.

In a multivariate linear regression analysis, the changes in 24-h SBP were the sole independent predictors of the changes in LVM. When 24-h SBP and 24-h DBP were forced into the same model, only 24-h SBP achieved significance. Similarly, when 24-h SBP and 24-h PP were forced into the same model, only 24-h SBP achieved significance, although 24-h PP bordered on statistical significance ($P=0.06$). The changes in body weight did not show any independent association with the changes in LVM. The percentage changes in LVM from the baseline to the follow-up visit could be predicted by the following equation: percentage changes in LVM = $0.73 \times (\text{percentage changes in 24-h SBP}) - 0.48$ ($P < 0.0001$). Thus, for any given reduction in 24-h SBP, the reduction in LVM did not show any association with the changes in DBP and PP, either clinic or ambulatory. The predicted values of the changes in LVM in relation to the changes in 24-h SBP and PP are shown in Figure 3.

Discussion

The present study provides further evidence that SBP is a major determinant of the development and regression of LVH in subjects with essential hypertension. Our findings mostly focused on

regression of LVH and for the first time provided a direct comparison between the serial changes in LVM and those in various BP components (systolic, diastolic, pulse) in a large population of subjects with essential hypertension who underwent 24-h ambulatory BP monitoring and echocardiography before and during antihypertensive treatment.

The fundamental role of SBP in the basic mechanisms leading to LVH is supported by several experimental data. The immediate cardiac consequence of a rise in SBP is an increase in end-systolic wall stress (ESWS) that triggers cellular reactions ultimately leading to an increase in the volume of each cardiac myocyte.¹⁶ This process is mostly due to addition of sarcomeres in parallel and the resulting increase in the cardiac mass tends to progressively normalize ESWS.¹⁶ This pattern is typical of prevalent or near pure pressure overload states such as hypertension and aortic stenosis.

However, the pathogenesis of LVH in hypertensive humans is more complex than expected by the above model, due to concurrent contribution of nonhaemodynamic factors (angiotensin, insulin and insulin growth factors, catecholamines, sodium intake, blood viscosity, overweight, genetic factors) that can contribute to stimulating cardiac muscle growth with mechanisms partially independent of BP.¹⁷⁻¹⁹ For example, in a group of never-treated hypertensive subjects who underwent noninvasive ambulatory BP monitoring (ABPM) and a 75-g oral glucose tolerance test, we found that LVM was independently accounted for by average 24-h SBP, gender, and body mass index, but also by insulin growth factor 1 and postload insulin ($R^2=0.64$).¹⁹ In another analysis of the PIUMA study conducted in 2545 untreated and unselected hypertensive subjects,⁸ after adjustment for the confounding effect of age, gender, body weight and duration of hypertension, the proportion of variability of LVM explained by SBP was greater than that explained by other BP components. When 24-h SBP and 24-h pulse pressure (PP) were forced into the same model, 24-h PP lost statistical significance.⁸

The ascendancy of SBP over PP in the regulation of LVM is plausible from several pathophysiological angles. The increase in LVM in essential hypertension is primarily related to the increase in ESWS, which includes SBP in its estimate. In this respect, the reported direct association between increased LVM and the augmented late systolic component of the pressure waveform, resulting from an earlier peripheral reflection wave, is likely to be mediated by an increased ESWS.

As far as regression of LVH is concerned, the degree of reduction in LVM during treatment has been associated more closely with the reduction in 24-h ambulatory BP than to that of clinic BP, probably because 24-h ambulatory BP better reflects

the BP load to which the LV is chronically subjected.²⁰ In 206 essential hypertensive subjects with LVH who underwent echocardiography and 24-h ABPM before and after 12 months of treatment based on an angiotensin-converting-enzyme inhibitor, the reduction in LVM was not significantly associated with the reduction in clinic BP, while it was significantly associated with the reduction in 24-h ambulatory BP ($r=0.42$ SBP and $r=0.38$ DBP).⁹ We obtained similar results in a smaller study of 88 subjects who underwent echocardiography and 24-h ABPM before and after treatment with losartan or enalapril.¹⁰ The reduction in LVM was associated with the reduction in 24-h ambulatory BP, not with the reduction in clinic BP.¹⁰ Overall, these data suggest that the reduction in LVM during treatment may be significantly affected by the reduction in BP, particularly by that in SBP, although serial measurements of clinic BP may be inadequate to reveal such an association. This view is supported by results of the left ventricular hypertrophy regression: indapamide vs enalapril (LIVE) study, where the degree of reduction in LVM after 1 year of treatment was greater with indapamide than with enalapril, despite a comparable BP reduction in the two groups.²¹ In the LIVE study, no significant correlation was found between the changes in clinic BP and those in LVM regardless of treatment ($r=0.080$ for SBP and 0.004 for DBP; both $P=NS$). However, the reduction in SBP was consistent in each treatment group, approximating $-31.6/-16.2$ mmHg indapamide group and $-28.6/-14.9$ in the enalapril group among the participants who completed the 1 year's monotherapy.

An unexpected finding in our study was the lack of association between the changes in LVM and those in body weight. In the Treatment Of Mild Hypertension Study (TOMHS), the serial changes in LVM over time showed a significant association with the changes in body weight and SBP in 844 patients with mild hypertension randomized to different antihypertensive regimens.²² However, in the TOMHS study, all patients received an aggressive behavioural and dietary intervention in addition to the study drugs, 20% were black, and a consistent proportion of these patients were overweight or frankly obese. In contrast, the mean body weight was only 75.2 kg in our population and only a few of these patients were obese. Thus, the disclosure of a significant independent relationship between LVM reduction and weight changes might critically depend on the anthropometric features and specific interventional procedures in the single study.

In conclusion, our study indicates that the reduction in SBP is the main determinant of the reduction in LVM in treated hypertensive subjects. In clinical trials and everyday practice, serial measures of clinic BP alone may be inadequate to establish the role of BP reduction for achieving LVH regression in hypertensive patients.

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