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ORIGINAL ARTICLE

Arterial hypertension increases left ventricular mass: role of tight blood pressure control

LA Ferrara[1], O Vaccaro[1], O Cardoni[2,†], M Mancini[1] and A Zanchetti[3]
[1]*Department of Clinical and Experimental Medicine, Federico 2nd University of Naples, Italy;* [2]*Ospedale di Gubbio;* [3]*Centro di Fisiologia Clinica ed Ipertensione, Università di Milano, Ospedale Maggiore and Istituto Auxologico Italiano, Milano, Italy*

In middle-age hypertensives from the Gubbio Population Study, we evaluated the relationship between blood pressure (BP) control over a long time and the prevalence of left ventricular hypertrophy (LVH). A population survey was performed in 1982–1985 and repeated in 1989–1992. During the second survey, subjects in the age range 40–60 years were invited to undergo an M-mode echocardiographic examination. A total of 487 subjects who participated in both surveys are included in the present analysis. Some of them (294) were normotensive (Group 1), 110 were hypertensive but had never taken antihypertensive drugs (Group 2), 47 hypertensives on drugs were in good BP control (Group 3) and 36 hypertensives on drugs had uncontrolled hypertension (Group 4). BP values at the 1989–1992 examination were, respectively, 122/77, 145/86, 124/78 and 153/91 mmHg, while 7 years earlier were 122/77, 133/84, 136/85 and 152/95 mmHg. Despite normal BP levels in Group 3, left ventricular mass index (LVMi, g/m$^{2.7}$) was greater than in normotensives (42.4 $\pm$ 10, 46.6 $\pm$ 13, 47.0 $\pm$ 10, 51.9 $\pm$ 15 g/m$^{2.7}$). Accordingly, the prevalence of LVH (LVMi $>$ 51 g/m$^{2.7}$) was 18, 26.4, 36.7 and 50% in groups 1–4, respectively. The 193 hypertensives were, thereafter, divided according to BP control (ie $<$ 140/90 mmHg) on both surveys (1983–1985 and 1989–1992): 27 hypertensives with optimal BP levels on both visits also had a ventricular mass similar to normotensives and significantly lower than the other hypertensives (LVMi 44.6 $\pm$ 11.6 vs 48.5 $\pm$ 13.2, $P<0.001$). In conclusion, these findings indicate that hypertensive patients with BP values at levels similar to those in normotensives for a long period do not increase their left ventricular mass in comparison to subjects with normal BP levels.
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Introduction

Arterial hypertension is frequently associated with target organ damage. Left ventricular hypertrophy (LVH), along with arteriosclerotic lesions in aortic, coronary, cerebral and renal vessels, is among the most frequently observed organ complications of hypertension.[1–5] While there is no doubt about the consequences of increased blood pressure (BP) values, it is still debated whether long-term treatment of hypertension and adequate BP control are able to prevent the development of LVH or induce its complete regression.

The aims of the present study were to investigate in subjects identified during a longitudinal population survey

(a) the prevalence of LVH among hypertensive and normotensive subjects, and
(b) to evaluate the effects of antihypertensive treatment on left ventricular mass (LVM), in hypertensive patients who had achieved a satisfactory BP control and in those without a satisfactory BP control.

These objectives were pursued in the Gubbio Population Study, in which the Gubbio population was first screened at the beginning of the 1980s and reviewed 7 years later.

Correspondence: Dr LA Ferrara, Department of Clinical and Experimental Medicine, Federico 2nd University of Naples, Via S. Pansini 5, Naples 80131, Italy.
E-mail: ferrara@unina.it
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†Deceased.
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Patients and methods

Study population

The Gubbio Population Study is a clinical survey performed in the small town of Gubbio, in the central part of Italy, in Umbria, not too far from Perugia. The study started in 1983–1985 when 5376 men and women, aged 5–90 years, were first examined; subsequently, they underwent a follow-up examination in 1989–1992.[6–7] In both surveys, the comprehensive examination included measurement of body weight, height, BP and heart rate (HR), a 12-lead electrocardiogram, standardized measurements of blood and urine laboratory tests, anthropometric variables, individual and family medical history and questionnaires on lifestyle and awareness of hypertension and other cardiovascular risk factors.[8] BP was measured by doctors trained by the Istituto Superiore di Sanità, Rome. Measurements were taken after the participant had been seated quietly for 5 min; pressure was taken on the right arm, with use of an appropriate cuff size. Three recordings were taken 1 min apart. The first and the fifth phases of Korotkoff sounds were defined systolic and diastolic pressure levels, respectively. Subjects with BP $\geqslant$140/90 mmHg were defined as hypertensives. After the second survey, all persons in the age range 40–60 years ($n=851$) were invited for an echocardiographic examination. The protocol of the study had been approved by the Ethic Committee and informed consent was obtained from all participants in the study.

Echocardiographic procedures

All echocardiograms were performed in 1990–1992 by the same echocardiographer (OC). Echocardiograms were obtained with participants lying in the left lateral decubitus position with the head at 30° from the horizontal. A Vingmed 700 ECHOcardiographic machine with a 3.5 MHz transducer was used. Pictures of M-mode left ventricle images were taken by a fibreoptic recorder on a light-sensitive paper at 50 mm/s. All examinations were recorded on a VHS videotape. Measurements of the interventricular septal thickness (IVST) and of the left ventricular posterior wall thickness (PWT) and of the left ventricular diastolic internal diameter (LVIDd) were taken at the mitral valve chordal level. The three cardiac cycles of the M-mode pictures were measured by a single reader (OC), and mean values were used to calculate the variables derived. LVIDd and end-systolic (LVIDs), PWT and IVST were measured according to the recommendations of the American Society of Echocardiography.[9]

A second set of measurements was also taken according to the Penn convention criteria to calculate LVM.[10] This was normalized for body height to the power of 2.7 (LVMi), an indexation that is independent of body weight and, therefore, has been shown to detect deviations from normality also in obese individuals,[11] and for body surface area (LVMs), which was calculated according to the Dubois formula.[12] The relative wall thickness (RWT), an index of LV geometric pattern, was measured at end diastole, as 2PWT/end diastolic diameter (EDD). LVH was defined as LVMi $>51\,g/m^{2.7}$,[13] LVH was defined as concentric when RWT was $\geqslant 0.44$.[14]

Fractional shortening (FS) was calculated according to the following formula:

$$FS = [(LVIDd - LVIDs/LVIDd)]100$$

All echocardiograms were read by the same operator and in a 20% sample of tracings, randomly chosen, intra-reader variability of the measurement was evaluated. The two measurements of each variable were closely related to each other ($P<0.001$) since the % error was 3.76 for ST, 4.28 for PWT and 1.06 for LVM.[15]

Statistical analysis

Data were analysed by using SPSS (SPSS Italia, Bologna, Italy) statistical package. They are expressed as mean $\pm$ standard deviation (M $\pm$ s.d.). Comparisons of means were performed by unpaired *t*-test and by one-way analysis of variance with Tukey's multiple comparisons. The strength of correlation between different variables was evaluated by Pearson's linear correlation; multiple regression analysis with stepwise forward procedure was used to explore the independent influence of some variables on LVM.

Results

Of the whole group of 851 middle-age individuals who underwent the echocardiographic examination, the present study included 550 who had comprehensive clinical visits both at the 1983–1985 and at the 1989–1992 surveys. At the time of the latter survey, the prevalence of hypertension in this group was 35% since 193 of these subjects were found to have systolic BP (SBP) value $\geqslant$140 and/or diastolic BP (DBP) $\geqslant$90 mmHg or were on antihypertensive medications. Only 83 (43%) of them were receiving antihypertensive drugs, and in this subgroup 47 patients (24.3% of the hypertensive population) were found under good BP control (ie BP $<$ 140/90 mmHg). Therefore the population sample was divided, according to the data at the 1989–1992 control, into four subgroups: Group 1 (357 normotensives, ie BP $<$ 140/90 mmHg), Group 2 (110 hypertensives who were not receiving antihypertensive medications), Group 3 (47 hypertensives who were receiving drugs and had well-controlled BP values, ie BP $<$140/90 mmHg) and Group 4 (36 hypertensives on antihypertensive treatment but with BP still above recommended values, ie with

BP $\geqslant$ 140/90 mmHg). As expected, normotensive subjects had a significantly lower body mass index (BMI) than hypertensives: in order to avoid the confounding influence of body weight on LVM, we included in the present analysis only normotensives with BMI in the same range of hypertensives. As a consequence, this report will deal with 294 of the 357 normotensive subjects.

The characteristics of the four subgroups are shown in Table 1: normotensives were only slightly younger than untreated hypertensives; normotensives and treated and well-controlled hypertensives had significantly lower SBP and DBP in comparison to the other two subgroups. A rather close relationship between BP values at the 1983–1985 and the 1989–92 visit was observed ($r = 0.505$ for SBP, $P < 0.01$; $r = 0.440$ for DBP, $P < 0.01$).

Echocardiographic findings are shown in Table 2: left ventricular mass index (LMVI), normalized either by body surface area or by height to the power 2.7, was significantly lower in normotensives in comparison to hypertensives. It is interesting to remark that patients in Group 3 had a significantly greater cardiac mass than normotensives despite their mean BP values being in the normal range. Their cardiac mass, however, was lower than that of treated hypertensives without good BP control, while no difference was found in comparison to untreated hypertensives. Accordingly, the prevalence of LVH, defined as LVMi $>51\,g/m^{2.7}$, was 18% (53/294) in normotensives, and 26.4% (29/110), 38.3% (18/47), 50% (18/36) in untreated, treated and well-controlled and treated, but uncontrolled hypertensives, respectively.

Linear correlation analysis showed a significant relationship between LVMi or LVMs and SBP or DBP values measured both at the 1983–1985 and 1989–1992 visit (Table 3). It is interesting to remark that the correlation coefficients were somewhat higher with BP values measured in 1982–1985, suggesting that the duration of hypertension was also important.

No drug-specific effect on LVM was detected since both subgroups, with and without well-controlled hypertension, received similar pharmacological treatment. Diuretics, alone or, more frequently, in combination with angiotensin-converting-enzyme (ACE) inhibitors, were the drugs most frequently used to lower BP in both subgroups (Table 4).

Table 1 Demographic characteristics of the Gubbio Population Sample, age 40–60 years, who had been seen at the 83–85 control and underwent echocardiographic examination

Parameters	*Normotensives* (n = *294*)	*Hypertensives* (n = *193*)		
		Untreated (n = *110*)	*Treated and well-controlled* (n = *47*)	*Treated and uncontrolled* (n = *36*)
Age (years)*	49.6 ± 2.8	50.7 ± 2.8[a]	50.6 ± 3.4	50.7 ± 2.8
BMI (kg/m²)*	28.3 ± 3.3	28.7 ± 4.3	29.1 ± 4.9	28.9 ± 4.4
SBP 89–92 (mmHg)*	119.6 ± 10.3	144.6 ± 22.6[a,b]	123.9 ± 10.7	153.1 ± 10.1[a,b]
SBP 83–85 (mmHg)*	122.3 ± 14.5	133.6 ± 16.4[a]	136.0 ± 13.1[a]	152.5 ± 20.5[a,b]
DBP 89–92 (mmHg)*	75.7 ± 6.8	86.1 ± 10.9[a,b]	77.9 ± 8.1[a]	91.0 ± 8.5[a,b]
DBP 83–85 (mmHg)*	76.9 ± 8.7	83.62 ± 11.4[a]	84.7 ± 7.9[a]	95.2 ± 9.0[a,b]

Significance between groups: *$P < 0.001$.
[a]Significance *vs* normotensives.
[b]Significance *vs* well-controlled hypertensives.

Table 2 Echocardiographic parameters of cardiac structure and systolic and diastolic function in the Gubbio Population Sample, age 40–60 years

Parameters	*Normotensives* (*n* = *294*)	*Hypertensives* (*n* = *193*)		
		Untreated (n = *110*)	*Treated and well-controlled* (n = *47*)	*Treated and uncontrolled* (n = *36*)
IVST***	9.2 ± 1.6	9.9 ± 2.1[a]	9.6 ± 1.3[a]	10.2 ± 1.65[a]
PWT**	9.0 ± 1.6	9.4 ± 1.8	9.2 ± 1.4	9.9 ± 1.3[a]
LVID(d)	48.2 ± 5.0	48.5 ± 4.1	49.4 ± 5.2	49.5 ± 6.8
LVMi (g/m²·⁷)***	42.4 ± 10.4	46.6 ± 12.6[a]	47.0 ± 10.0[a]	51.9 ± 15.5[a]
LVMs (g/m²)***	86.6 ± 20.7	93.4 ± 22.8[a]	94.3 ± 20.7[a]	103.3 ± 26.5[a,b]
RWT (%)*	37.7 ± 7.4	39.1 ± 7.9	37.5 ± 6.6	40.9 ± 7.5
FS (%)*	37.5 ± 6.8	40.1 ± 6.6[a]	39.2 ± 6.9	38.2 ± 8.3[a]

Significance between groups: *$P < 0.05$ **; $P < 0.01$; ***$P < 0.001$.
[a]Significance *vs* normotensives.
[b]Significance *vs* controlled hypertensives.

In order to evaluate the impact of the duration of the optimal BP control on LVM, the population of 193 hypertensives was also divided according to BP control at the two visits in a subgroup of 166 hypertensives with BP values equal or above 140/90 mmHg in at least one of the two surveys and a smaller group of 27 hypertensives with BP values within normal limits in both visits. Groups were comparable for age (51.0 ± 2.9 *vs* 50.0 ± 3.4 years) and BMI (29.2 ± 4.6 *vs* $28.9 + 4.2$), while BP was significantly lower in the well-controlled group ($149/88 \pm 18/10$ *vs* $121/77 \pm 11/8$ mmHg, $P < 0.001$), with no difference in comparison to normotensives. Echographic parameters of cardiac structure in the well-controlled group were similar to those of normotensives and significantly lower than those of the other hypertensive subgroup (Table 5). All hypertensives under optimal control were receiving antihypertensive drugs (ACE inhibitors and diuretics, mainly) at the 1989–1992 follow-up, while six of them had been off antihypertensive drugs at the 1983–1985 visit.

Discussion

It is well known that there is a close relationship between LVM and BP values: accordingly, the prevalence of LVH is much higher in the hypertensive than the general population.[16] The present investigation aimed at evaluating the influence of long-term BP control on LVM and prevalence of LVH in a population sample of both sexes in the age range 40–60 years. The major limitation of the present study is the lack of echocardiographic measurements at the time of the first examination. This absence prevented us from evaluating possible longitudinal changes in LVM and only allowed us to investigate about the relationship between LVM and BP values measured at the time of the two surveys. The findings of the present study deserve some comments.

Firstly, the prevalence of hypertension in this middle-age sample of the general population of an Italian city is rather high, averaging 35%. Recent epidemiological data indicate that in Italy the prevalence of hypertension averages 24% in the 40–50 years decade and 35% in the 50–60 years decade:[17] therefore the prevalence in Gubbio seems to be slightly higher than in other areas of Italy. This might be related to the high prevalence of overweight and frank obesity in the study population with a BMI ranging from 27.2% in normotensives (when all 357 normotensives were included) to 29.1% in treated and well-controlled hypertensives.

Table 3 Correlation coefficients between SBP or DBP and LMVi to height to the power 2.7 or to body surface area

	LVM ($h^{2.7}$)	*LVM (area)*
SBP 1983–1985	0.303*	0.289*
SBP 1989–1992	0.269*	0.215*
DBP 1983–1985	0.206*	0.243*
DBP 1989–1992	0.183*	0.162*

Significance: *$P < 0.001$.

Table 5 Echographic parameters of cardiac structure in the hypertensive population of the Gubbio Study, age 40–60 years, according to the optimal BP control at the two follow-ups (1983–1985, 1989–1992)

Parameters	*Hypertensives not under optimal control (n = 166)*	*Hypertensives under optimal control (n = 27)*
IVST (mm)	10.0 ± 2.0*	9.4 ± 1.4
PWT (mm)	9.7 ± 1.7*	8.8 ± 1.3
LVID(d) (mm)	49.0 ± 5.1	49.4 ± 5.2
LVMi ($g/m^{2.7}$)	48.5 ± 13.2*	44.6 ± 11.6
LVMs (g/m^2)	97.0 ± 23.5*	89.0 ± 22.2
RWT (%)	39.7 ± 7.8*	36.9 ± 6.1

*Significance: $P < 0.001$.

Table 4 Drugs used in the normotensive and hypertensive individuals in the Gubbio Population Sample at the 83–85 and 89–92 control

Drugs	*Normotensives (n = 294)*		*Hypertensives (n = 193)*					
			Untreated (n = 110)		*Treated and well-controlled (n = 47)*		*Treated and uncontrolled (n = 36)*	
	83–85	89–92	83–85	89–92	83–85	89–92	83–85	89–92
No drug	283	294	90	79	26		16	
ACE inhibitors						5		8
β-blockers					1	6	1	5
Nifedipine						6		4
Verapamil								2
Central acting drugs			1		1		2	
Vasodilators					2		1	
Diuretics			7		4	12	6	5
Diuretics+ACE inhibitors			1		13	18	9	10
Digitalis	2		1					2
Benzodiazepines	9		10	31			1	

The second comment regards the BP control in this population sample. In all, 43% of hypertensives received antihypertensive medications and a good BP control was only achieved in 25% of all hypertensives. The prevalence of well-treated hypertensives is similar to that observed in other countries, like US in the NHANES,[18] and also in other Italian areas, like in the city of Monza where it averaged 28%.[19] It is interesting to stress, however, that the comparison of the BP measurements made in our patients in 1983–1985 and 1989–1992 indicates that BP control markedly improved, with a significant reduction by −13/−7 mmHg in SBP and DBP values in Group 3 and a slight BP reduction in Group 4 (−1/−4 mmHg). Patients who did not receive antihypertensive drugs, on the other hand, showed an increase in their BP by 13/2.5 mmHg. The data reported here agree with a similar BP trend reported in the whole Gubbio population.[7]

The third point to be discussed is the high prevalence of LVH in our study. It might be suggested that this is related, at least in part, to the high prevalence of overweight or frank obesity. The independent influence of high BP values, however, is underlined by its relationship with LVM corrected by body surface area, which adjusts the mass of the left ventricle by body weight. Although in agreement with other studies,[20] hypertensive patients under good BP control at the 1989–1992 follow-up had lower LVM than uncontrolled hypertensives; their ventricular mass was, however, still significantly higher than that of normotensives. This suggests that even full normalization of BP values might be unable to LVH entirely regress, a component of which might be irreversible. Moreover, the use of antihypertensive drugs that were shown to be less effective in reducing LVM might be responsible for this finding.[21] Alternatively, regression may require a longer duration of BP normalization before LVM returns to a normal status. The cross-sectional nature of this study allows us only to speculate regarding this point. However, the last hypothesis is supported by the observation that in the small group of hypertensives with a presumedly optimal BP control over the 7-year follow-up (they were on antihypertensive treatment on both visits and had well-controlled BP) the difference in the structure of the left ventricle was small and did not reach statistical significance in comparison to normotensives. Accordingly, a meta-analysis of 39 studies of randomized double-blind antihypertensive treatment showed that the duration of treatment was significantly associated with the magnitude of LVMi decrease.[22]

Optimal treatment of hypertension, therefore, might induce a time-dependent beneficial influence on LVM, which might explain the discrepancies in the results of different studies. Long-lasting maintenance of BP values within the normal range might be able to affect favourably cardiac complications either preventing the development of LVH or inducing its complete regression, while BP control for a shorter period might apparently fail to normalize LVM fully.

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