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ORIGINAL ARTICLE

Left ventricular concentric remodelling and extracardiac target organ damage in essential hypertension

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Left ventricular (LV) concentric remodelling is an adaptive change in cardiac geometry frequently observed in arterial hypertension. This study was addressed to investigate the extent of extracardiac target organ damage (TOD) in patients with LV concentric remodelling. Two groups of never-treated essential hypertensives, 31 with normal LV geometry (group I, relative wall thickness: 0.39) and 31 with LV concentric remodelling (group II, relative wall thickness: 0.47) matched for age, sex, body mass index and mean 24-h systolic blood pressure (BP), were included in the study. They underwent clinical and laboratory examination, 24-h ambulatory BP monitoring (ABPM), 24-h urinary collection for microalbuminuria, non-mydriatic photography of ocular fundi, echocardiography and carotid ultrasonography. In both groups age (I: 51 ± 11 years; II: 51 ± 11 years), body mass index (I: 25 ± 3 kg/m^2; II: 26 ± 3 kg/m^2), clinic and 24-h ABPM values (I: 149 ± 11/95 ± 8, 142 ± 11/91 ± 7 mm Hg; II: 150 ± 11/98 ± 9, 142 ± 12/92 ± 9 mm Hg) were similar by design. There were no differences between patients with normal LV geometry and with LV concentric remodelling in LVM index (97 ± 16 *vs* 99 ± 16), carotid intima-media thickness (0.7 ± 0.02 *vs* 0.7 ± 0.02) and carotid plaques prevalence (35% *vs* 35%). Furthermore, no significant differences among the two groups were found in the prevalence of retinal changes and microalbuminuria. These results suggest that in hypertensive patients with similar BP and LVMI levels, LV concentric remodelling is not associated with more prominent TOD.
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Introduction

Left ventricular hypertrophy (LVH) diagnosed by electrocardiographic or echocardiographic criteria has been demonstrated to be a powerful predictor of increased morbidity and mortality in hypertensive patients and in the general population.[1,2] A large number of studies have shown that the left ventricle may respond to a chronic increase in blood pressure (BP) levels by developing three different abnormal geometric patterns: concentric or eccentric LVH and concentric LV remodelling.[3–5] Recent prospective studies have indicated that a stepwise increase in risk of cardiovascular morbidity and mortality occurs from a low event rate in hypertensive patients with normal LV mass and geometry, to intermediate rates in those with eccentric LVH, and to the highest level of risk in patients with concentric LVH.[6,7] The gradient in cardiovascular risk among patients with different LV geometric patterns seems to be related to several factors including the level of LV mass itself, cardiac function and systemic haemodynamic profiles.[8–10] Furthermore, a close association between LVH and other markers of target organ damage (TOD) has been demonstrated.[11,12] LV concentric remodelling secondary to hypertension is a subtle and early change in cardiac geometry characterised by increased LV relative wall thickness (RWT) with normal overall muscle mass, which seems to be associated with a greater cardiovascular risk than is the normal LV geometry pattern.[13] Since the excess of risk in this altered geometric pattern could be related to the concomitant development of macrovascular and microvascular structural and functional alterations, the present study was specifically designed to evaluate whether in recently diagnosed essential hypertensives the presence of LV concentric remodelling represents the earliest and only change in cardiovascular system or whether the increase in RWT is associated with parallel abnormalities in extracardiac TOD.

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Patients and methods

From 225 consecutive, never treated hypertensive patients with normal LV mass referred for the first time to our outpatient clinic by their general practitioners, we selected 31 subjects with LV concentric remodelling and 31 subjects with normal LV geometry, matched for sex, age (within 2 years), body mass index (within 10%), smoking habit, mean 24-h systolic and diastolic BP (within 5 mm Hg) and serum lipid values (within 10%). They fulfilled the following admission criteria: (1) recent (<2 years) diagnosis of grade 1 and 2 hypertension; (2) absence of secondary hypertension, congestive heart failure, previous myocardial infarction, cardiac valve diseases, history of coronary by-pass, diabetes mellitus and conditions preventing technically adequate ambulatory BP monitoring (ABPM) (eg atrial fibrillation); (3) good quality of echocardiographic and carotid ultrasonographic examinations. After informed consent had been obtained during the initial visit, all patients were subjected to the following procedures: (1) routine blood chemistry; (2) 24-h urinary collection for microalbuminuria; (3) non-mydriatic retinography; (4) 24-h ABPM; (5) echocardiography; and (6) carotid ultrasonography.

Definition of groups

Patients included in the study had a normal LV mass (<134 g/m^2 in men; <110 g/m^2 in women). They were divided into two groups: those with normal LV geometry and those with LV concentric remodelling, the latter defined by a RWT $\geqslant$0.45. This partition value has been reported in several studies to be of clinical and prognostic relevance in arterial hypertension.[14]

Clinic BP measurement

BP was measured, during the morning (between 10 and 12 am) in the outpatient clinic by a physician using a mercury sphygmomanometer (1st and 5th phases of Koroktoff sounds taken as systolic and diastolic BP, respectively) after the subjects had rested for 5–10 min in the sitting position. Three measurements were taken at 1-min intervals, and the average used to define clinic BP.

Ambulatory BP monitoring

Twenty-four hour ABPMs were carried out on the non-dominant arm using a Spacelabs 90207 device (Spacelabs Inc, Richmond, WA, USA) after validation of its readings against those of a mercury sphygmomanometer by means of an Y tube.[15] The device was set to obtain BP readings at 15-min intervals during the day (7 am to 11 pm) and at 20-min intervals during the night (11 pm to 7 am). The patients were asked to attend their usual daily activities but to keep still at the times of measurement, to note the occurrence of unusual events or of poor night sleep in a diary and to go to bed no later than 11 pm. The BP monitorings were always performed over a working day (Monday through Friday). Each ABPM dataset was first automatically scanned to remove artefactual readings according to preselected editing criteria. The recording was then analysed to obtain 24-h, daytime and night-time average systolic, BP, diastolic BP and heart rate.

Echocardiography

M-mode, two-dimensional and Doppler echocardiographic examinations were carried out with subjects in the partial left decubitus position using a commercially available instrument (ATL HDI 3000, Bothell, WA, USA) equipped with a 2.25 MHz imaging transducer. End-diastolic and end-systolic left ventricular internal diameters (LVIDd, LVIDs), interventricular septum (IVST) and posterior wall thicknesses (PWT) were calculated from two dimensionally guided M-mode tracing and measured during five consecutive cycles according to the Penn Convention.[16] Left ventricular mass was estimated by Devereux's formula and normalised by body surface area,[17] and RWT calculated as $2 \times$ PWT/LVIDd. A normal LV mass was defined as a mass <134 g/m^2 in men and <110 g/m^2 in women.[18] Left ventricular filling was assessed by recording mitral flow velocity by the standard pulsed Doppler technique; the following parameters were considered: the early diastolic peak flow velocity (E), the late diastolic peak flow velocity (A) and the ratio of the early to late flow velocity peaks (E/A ratio).[19]

Carotid ultrasonography

Imaging of the right and the left extracranial carotid arteries was obtained by a high resolution linear array 10 MHz probe, with the patients supine with slight hyperextension of the neck. The end-diastolic intima-media thickness (IMT) of the posterior (far) wall of both common carotid arteries and the lumen diameter were measured 5, 10, 15, 20, 25, 30 mm caudally to the bulb and the measurements averaged. The IMT was calculated on two-dimensional longitudinal sections of the carotid artery as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line according to the methods of Pignoli *et al*[20] and Salonen *et al*.[21] A plaque was defined as presence of a focal thickening greater than 1.3 mm in any segment of either carotid artery.[22] IM thickening was diagnosed when common carotid IMT exceeded 0.8 mm.[23] As previously reported in our laboratory the intraobserver and the interobserver coefficients of variation for LV mass index are 7.4% and 8.6%, respectively, and for common carotid IMT 9.2% and 10.1%.[24,25]

Retinography

All subjects underwent a bilateral non-mydriatic retinography (Topcon TRC-NW$_3$). Images were captured using an analogic camera (Topcon MT-1), set in order to obtain two photographs, centered on the macula.[25] The images, printed on professional film (Polaroid 779 High Speed Color Film ISO 640 (29°)) were immediately examined for quality (further photographs were taken if necessary) and were evaluated by two physicians, who had no knowledge of the patients clinical characteristics, using this simplified Keith, Wagener and Barker (KWB) classification:[26] I—Diffuse arteriolar narrowing: an arteriovenous ratio of at least 1:2; II—Abnormal arteriovenous crossing: any degree of depression of the vein in a crossing situated at more than one papillar diameter from the papilla. The interobserver coefficients of variation were 26 and 23% for the assessment of diffuse arteriolar narrowing and abnormal arterio-venous crossing, respectively.

Microalbuminuria

Twenty-four hour urinary albumin concentration was measured by a commercially available radioimmunoassay kit (Sclavo SPA, Cinisello Balsamo, Italy). The detection limit of the method was 0.5 mg/l. Microalbuminuria was defined as a urinary albumin excretion (UAE $\geqslant$30 mg/24 h and $<$300 mg/24 h).

Statistical analysis

Values are expressed as means ± s.d. Mean values between groups were compared by Student's *t*-test for independent samples and Mann-Whitney U test. Chi square statistics were used to compare categorical variables between groups. Correlations were obtained by using Pearson's equation. $P < 0.05$ was considered statistically significant.

Results

Study population

Clinical and laboratory characteristics of the study population are reported in Table 1. Age and sex distribution, body mass index, smoking habit, glucose, creatinine, and serum lipids did not differ significantly between the two groups by design. BP values are shown in Table 2. Clinic seated BP values were not different in patients with and without concentric remodelling (150/98 *vs* 149/95 mm Hg respectively). Average 24-h, daytime and night-time BP were similar in the two groups.

Cardiac structure and function

Subjects with LV concentric remodelling had smaller LV diastolic and systolic cavity dimensions and thicker interventricular septum and posterior wall and, by definition higher RWT (0.47 *vs* 0.43, $P < 0.01$) than subjects with normal ventricular geometry (Figure 1). Despite these differences in LV structure, LV mass and LV mass indexed by body surface area did not differ between the two groups. The endocardial fractional shortening and early/late mitral flow velocity ratio, which are indexes of systolic and diastolic function respectively, were superimposable in the two groups (Table 3).

Table 1 Clinical characteristics of patients with normal geometry and LV concentric remodelling

	Normal geometry (n = 31)	*LV concentric remodelling (n = 31)*	*P*
Age (years)	51 ± 11	51 ± 11	NS
Gender (M/F)	20/11	20/11	NS
BSA (m^2)	1.84 ± 0.24	1.83 ± 0.24	NS
BMI (kg/m^2)	25 ± 3	26 ± 3	NS
Smokers (%)	20%	32%	NS
Total cholesterol (mmol/l)	6.2 ± 1.03	6.2 ± 1.24	NS
HDL cholesterol (mmol/l)	1.08 ± 0.28	1.11 ± 0.28	NS
Tryglycerides (mmol/l)	1.58 ± 0.91	1.59 ± 1.25	NS
Glucose (mmol/l)	5.3 ± 0.49	5.4 ± 0.72	NS
Creatinine (μmol/l)	79.6 ± 20.3	79.6 ± 15.9	NS

BSA = body surface area; BMI = body mass index; HDL = high density lipoprotein; NS = not significant.

Table 2 Blood pressure and heart rate measurements in patients with normal geometry and with LV concentric remodelling

	Normal geometry (n = 31)	*LV concentric remodelling (n = 31)*	*P*
Systolic blood pressure (mm Hg)			
Clinic	149 ± 11	150 ± 17	NS
24-h average ABPM	142 ± 11	142 ± 12	NS
Daytime ABPM	148 ± 12	147 ± 12	NS
Night-time ABPM	129 ± 13	128 ± 13	NS
Diastolic blood pressure (mm Hg)			
Clinic	95 ± 8	98 ± 9	NS
24-h average ABPM	91 ± 7	92 ± 9	NS
Daytime ABPM	96 ± 8	97 ± 10	NS
Night-time ABPM	79 ± 9	80 ± 10	NS
Heart rate (beats/min)			
Clinic	76 ± 11	76 ± 11	NS
24-h ABPM	76 ± 10	77 ± 8	NS

ABPM = ambulatory blood pressure measurement; NS = not significant.

Extracardiac target organ damage

Results of carotid studies are summarised in Table 4 as means of measurements taken on the right and left sides. The average of IMT of the far wall of the common carotid artery, the arterial lumen diameter and the RWT were similar in the two groups. The

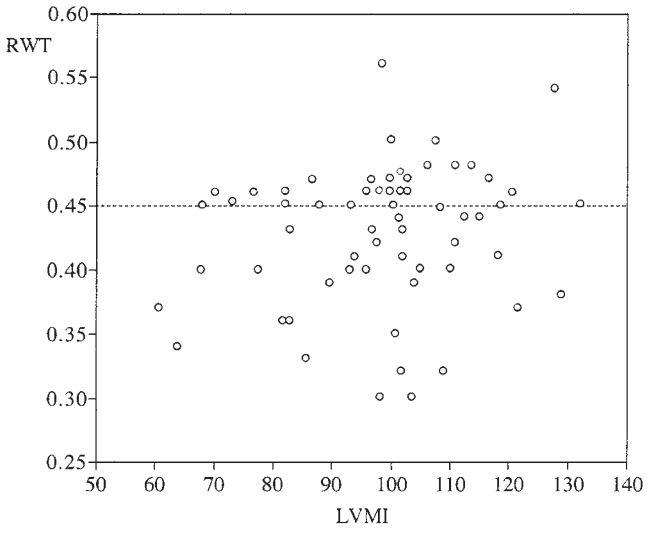

Figure 1 Relative wall thickness (RWT) and left ventricular mass index (LVMI) in hypertensive patients with normal left ventricular geometry and left ventricular concentric remodelling,

Table 3 Left ventricular structure and function in hypertensive patients with normal geometry and with LV concentric remodelling

	Normal geometry (n = 31)	*LV concentric remodelling (n = 31)*	*P*
LVIDd (mm)	48 ± 4	44 ± 3	<0.001
LVIDs (mm)	29 ± 5	26 ± 3	<0.004
IVSTd (mm)	9.6 ± 1	10.8 ± 1	<0.0001
PWTd (mm)	9.1 ± 1	9.9 ± 0.7	<0.0002
RWT	0.39 ± 0.4	0.47 ± 0.3	<0.0001
FS (%)	37 ± 4	36 ± 5	NS
E/A ratio	1.2 ± 0.4	1.1 ± 0.3	NS
LVM (g)	181 ± 40	183 ± 36	NS
LVMI (g/m^2)	97 ± 16	99 ± 16	NS

LVId = end-diastolic left ventricular internal dimension; LVIDs = end-systolic left ventricular internal dimension; IVSd = end-diastolic interventricular thickness; PWTd = end-diastolic posterior wall thickness; RWT = relative wall thickness; FS = fractional shortening; LVM = left ventricular mass; LVMI = left ventricular mass index; E/A ratio = early to late mitral flow velocity ratio; NS = not significant.

prevalence of IM thickening and carotid plaques did not differ in patients with normal or altered LV geometry. A similar prevalence of initial retinal changes (KWB I and II) were found in study and in control group. Finally, the mean urinary albumin excretion and the percentage of microalbuminuric subjects tended to be higher in patients with LV remodelling than in those with normal LV geometry, but this differencec did not attain statistical significance (Table 4).

Correlations between LV mass RWT, carotid IMT and microalbuminuria

No significant correlations were found between LVMI, and common carotid IMT ($r = 0.12$, $P = 0.3$) or microalbuminuria ($r = 0.10$, $P = 0.5$) in the entire cohort of 62 hypertensives. A similar nonsignificant trend was observed in the relations between RWT, and carotid IMT ($r = 0.07$, $P = 0.6$) or microalbuminuria ($r = 0.12$, $P = 0.2$).

Table 4 Extracardiac target organ damage in patients with normal geometry and with LV concentric remodelling

	Normal geometry (n = 31)	*LV concentric remodelling (n = 31)*	*P*
Carotid arteries			
CCA IMT (mm)	0.7 ± 0.02	0.7 ± 0.02	NS
CCA diameter (mm)	6.2 ± 0.9	6.2 ± 0.8	NS
RWT	0.23 ± 0.04	0.23 ± 0.05	NS
Prevalence of thickening (%)	22.5	25.8	NS
Prevalence of plaques (%)	35.4	35.4	NS
Retinal changes			
KWB I (%)	19.3	22.5	NS
KWB II (%)	32.5	32.5	NS
Renal involvement			
Mean UAE (mg/24 h)	9 ± 9	14 ± 12	NS
Prevalence of microalbuminuria (%)	3.2	6.4	NS

CCA = common carotid artery; RWT = relative wall thickness; KWB = Keith Wagener Barker; NS = not significant.

Discussion

The principal finding of the present study is that the carotid, retinal and renal involvement is similar in patients with LV concentric remodelling and with normal cardiac geometry despite a markedly increased RWT in the LV concentric remodelling group. To our knowledge this is the first study to show a lack of significant association between LV concentric remodelling and other signs of extracardiac TOD, such as carotid structural alterations, retinal changes and microalbuminuria in essential hypertensive patients. This is a notable finding and raises two important issues, concerning both prognostic and clinical implications of LV concentric remodelling detection in everyday practice. Firstly, it has been demonstrated that in hypertensive patients the abnormal patterns of LV geometry are related to different phatophysiological mechanisms and cardiovascular risk profiles. Koren *et al*[6] reported that the hypertensive patients with concentric LVH had the highest risk of mortality, followed by patients with eccentric LVH and LV concentric remodelling. The adverse prognostic significance of concentric remodelling of the left ventricle in hypertensive individuals with normal LV mass was confirmed by Verdecchia *et al*[8] in a large prospective study. However, Krumholz *et al*[7] in a population-based sample survey showed that the association between cardiac geometry and prognosis is largely

attenuated by adjustment for baseline differences in LV mass index. Another recent study, by Ghali *et al*[27] in patients with and without coronary artery disease showed that LV mass, but not its geometric pattern provided prognostic value. This clinical evidence suggest that LV mass *per se* is probably more important than LV geometry in predicting cardiovascular events. The second issue whether LV geometry is an independent predictor of extracardiac TOD in the general population and in hypertensive individuals has been addressed by several studies investigating vascular changes in subjects with different patterns of LV geometry.[28,29] In a cross-sectional study, conducted in a middle-aged general population in northern Italy, Muiesan *et al*[30] did not observe any involvement in carotid arteries in subjects with concentric remodelling. Only a limited number of studies have been addressed to specifically compare the extent of extracardiac TOD in never-treated essential hypertensive patients with LV concentric remodelling and normal LV geometry. Pierdomenico *et al*[31] found that IMT of carotid arteries was significantly lower in hypertensive subjects with normal LV geometry than in those with LV concentric remodelling. This difference, however, may be explained by the lower ambulatory BP and LV mass index values in hypertensive subjects with normal LV geometry. Our group reported that patients with concentric remodelling had parallel structural changes in large conductance arteries, in terms of a higher prevalence of carotid intima-media thickening and plaques compared to patients with normal geometry.[32] Also in this previous study clinic and 24-h systolic and diastolic BP levels and LV mass index values were significantly higher in subjects with LV concentric remodelling. In the present study, in contrast, not only the demographic and metabolic characteristics are superimposable in patients with and without LV concentric remodelling but also clinic, ambulatory BP, absolute LV mass and LV mass index values are similar in the two groups. The LV structure in our patients with concentric remodelling, was characterised by three main findings compared to those with normal geometry: (1) higher LV parietal thickness, (2) reduced LV diameters, and (3) virtually identical cardiac mass levels. Despite the differences in primary parameters of the LV, the indices of systolic (fractional shortening) and diastolic (LV filling profile) function did not differ between the groups. These results on LV function are substantially in agreement with data obtained in previuos echocardiographic studies of patients with LV concentric remodelling.[33,34] In addition to similar cardiac systolic and diastolic function, we documented a similar prevalence of extracardiac signs of TOD, such as carotid structural changes, initial retinal abnormalities and microalbuminuria, in patients with altered LV geometry compared to subjects with normal LV geometry. This finding represents a new piece of information on the relationship between LV concentric remodelling and macro and microvascular changes in arterial hypertension; this may be reasonably explained, considering that the most important factors associated with the development and progression of TOD such as demographic and clinical variables, BP and LV mass were similar in the two groups. In conclusion, our study suggests that initial structural changes in the heart may not necessarily parallel macro and microvascular alterations in the early phase of essential hypertension and that the impact of relative wall thickness of the LV *per se* in predicting extracardiac manifestations of TOD is not as strong as LV mass.

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