CROATIAN MEDICAL JOURNAL
CMJ

43(6):672-679,2002

CLINICAL SCIENCES

Effects of Four Antihypertensive Monotherapies on Cardiac Mass and Function in Hypertensive Patients with Left Ventricular Hypertrophy: Randomized Prospective Study

Drago Rakić, Zvonko Rumboldt, Jugoslav Bagatin, Stojan Polić

Department of Internal Medicine, Split University Hospital and School of Medicine, Split, Croatia

Aim. To compare the effects of four antihypertensive drugs, which have reportedly different effectiveness in reducing myocardial mass.

Methods. A randomized, double-blind, prospective study included 80 hypertensive patients with left ventricular (LV) hypertrophy confirmed both electrocardiographically and echocardiographically. We investigated the effects of indapamide, nicardipine, propranolol, and chlorthalidone on arterial blood pressure and LV mass and function.

Results. Sixty-four patients (34 men and 30 women) completed the 6-month study. No significant differences in antihypertensive effects of the four medications were found. The average decrease in systolic and diastolic blood pressure was 12.8% and 10.4%, respectively. All four antihypertensive medications caused pronounced reduction in LV mass, between 7.9% in the propranolol group and 10.1% in the nicardipine group, with no significant difference between the groups. In patients receiving diuretics, predominant decrease was observed in LV mass and LV mass index. In patients treated with propranolol, the thickness of both the LV wall and interventricular septum was reduced, whereas the reduction in LV mass, LV wall and interventricular septum thickness was found in patients treated with nicardipine. There was no significant correlation between the changes in LV mass and other variables (blood pressure, and systolic and diastolic function). Systolic function did not improve with the reversion of LV hypertrophy in any group of patients, but improvement was observed in some indices of diastolic function. The early and late LV filling velocity and their ratio did not improve significantly, either. Clinically relevant side effects were not observed.

Conclusion. All four antihypertensive monoterapies achieved a comparable control of hypertension and reduction in LV hypertrophy.

Key words: *antihypertensive agents; echocardiography; hypertension; hypertrophy, left ventricular*

Left ventricular hypertrophy, as diagnosed by electrocardiography (ECG) (1) and ultrasound (2), is associated with increased cardiovascular morbidity and mortality (1-3), increased risk of coronary heart disease (1,4), heart failure (5), sudden death (6), and ventricular arrhythmias (7). In hypertensive patients with left ventricular hypertrophy, systolic function remains preserved for a while (8), whereas diastolic dysfunction develops sooner (9).

Most antihypertensives reduce left ventricular mass in hypertensive patients with left ventricular hypertrophy, but they are not all equally effective, even when blood pressure reduction is comparable. For instance, vasodilator drugs lack this effect, whereas angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, and beta-blockers reduce left ventricular hypertrophy (10,11). The claims that diuretics do not reduce left ventricular mass are rare (12), and there is more evidence that under these circumstances left ventricular mass reduction exceeds the wall thinning (10,13). Indapamide also causes the reduction in left ventricular mass (14). Beta-blockers mostly reduce left ventricular wall thickness and improve systolic function, but their effect on diastolic function is controversial (10,11,15). Calcium channel blockers reduce left ventricular mass and improve myocardial relaxation, ie, diastolic function (11,16).

Because of such discordant findings of published reports, the aim of this study was to compare the effects of indapamide, nicardipine, propranolol, and chlorthalidone on arterial blood pressure and left ventricular mass and function in hypertensive patients with left ventricular hypertrophy.

Patients and Methods

Patients

Eighty inadequately treated or newly discovered hypertensive patients of both sexes, aged between 20 and 75 years, with diastolic blood pressure of 95-115 mm Hg and ECG evidence of left ventricular hypertrophy (17) were recruited in a randomized,

double-blind, prospective clinical study with between-group and within-group comparisons. The defined criteria for antihypertensive drug evaluation were applied from the beginning of the study (18). After obtaining informed consent, a detailed medical history was taken from each patient and physical examination performed, including blood pressure measurements and standard ECG. Echocardiographic examination was performed during a two-week placebo run-in period. Patients with definite left ventricular hypertrophy (left ventricular mass index >134 g/m^2 in men, and >110 g/m^2 in women) (19,20) were included in the study and randomized (sealed envelopes containing drugs' names) in four groups. The first group received indapamide, 2.5 mg once daily; the second group received nicardipine 20 mg thrice daily; the third group received propranolol 40 mg thrice daily, and the fourth group received chlorthalidone, 25 mg once daily, during 6 months. After the first, third, and sixth month (labeled as M1, M3, and M6), patients had their blood pressure and heart rate measured. Echocardiographic examination was performed at the beginning and at the end of the study (at M0 and M6) (Fig. 1).

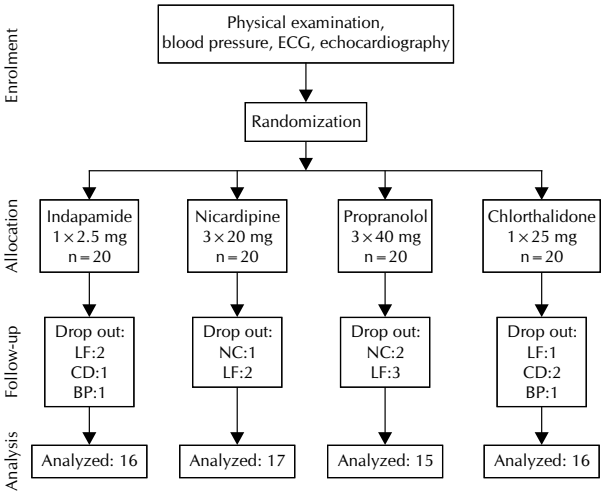

Figure 1. Flow chart of the patients in the study. NC – noncompliance, LF – failure to undergo examinations in early phase of study, CD – development of serious concomitant disease, BP – unsatisfactory blood pressure, ECG – electrocardiography.

Methods

Blood pressure was measured on the right upper arm with a mercury sphygmomanometer in the supine position and expressed in mm Hg. Out of 3 measurements, the mean value of the last two was recorded on the basis of the first and fifth phase of the Korotkoff sounds for systolic and diastolic pressure, respectively. The same investigator performed all the measurements, always between 8 and 10 a.m. In addition, at the beginning of the study, 20 patients divided in four groups with five patients each, had their blood pressure recorded continuously (ambulatory blood pressure monitoring, ABPM) over a 24-h period in 30-min intervals with an automatic device (SPS 1558; Sandoz Pharma, Basle, Switzerland).

Romhilt-Estes point score system was used in ECG evaluation of left ventricular hypertrophy (17). Echocardiographic examinations were performed on Ultramark 8, Advantage technology laboratory (ATL, Solingen, Germany) instrument with a 3 MHz transducer, a parasternal short axis view, and M-mode cursor positioned at two-dimensional image. Patients were lying on their left side, with the head of the bed elevated at 30°. At least 5 cardiac cycles were recorded at a speed of 50 mm/s. According to the Penn convention (19), the left ventricular internal diameter was measured at the end of systole and diastole, whereas the thickness of the interventricular septum and left ventricular posterior wall were measured at the end of diastole, during expiration, just below the mitral valve leaflet. These data were used to calculate left ventricular mass, left ventricular mass index (g/m^2 of the body surface), and systolic function parameters: ejection fraction (EF) and left ventricular fractional shortening (FS%) (19,20). Left ventricular hypertrophy was diagnosed when left ventricular mass index was greater than 134 g/m^2 in men and 110 g/m^2 in women (19). The left ventricular diastolic function was assessed with Doppler ultrasound by measuring isovolumetric relaxation time (IVRT; the time interval between the clicks of aortic valve closure and mitral valve opening), maximum early left ventricular filling velocity (peak E), maximum atrial left ventricular filling velocity (peak A), their ratio (E/A), and deceleration time (DT) of the E wave (21). Echocardiographic examinations were performed by two investigators: D.R. (80%) and S.P. (20% of the interventions). Both investigators were blinded to the studied antihypertensives, earlier echocardiograms, and other patient data.

The untoward effects noticed either by the investigators or by patients, reporting when asked or spontaneously, were recorded on a special list.

Statistical Analysis

The results were tabulated and presented as arithmetic means with 95% confidence intervals (CI). Kruskal-Wallis or Friedman`s analysis of variance, Wilcoxon`s two sample, and Mann-Whitney test were used where appropriate, with significance level set at $p<0.05$ (22). For multiple regression analysis of changes in left ventricular mass index vs blood pressure and for graphics, StatWorks computer program for Macintosh and Microsoft Excel 2000 for PC were used.

Results

Baseline Characteristics

Out of 80 patients included in the study (34 women and 46 men), 64 completed the trial (30 women and 34 men): 16 indapamide, 17 nicardipine, 15 propranolol, and 16 chlortalidone (Fig. 1). The mean±SD age of the patients who concluded the study was 50.4±10.0 years, and their mean±SD body mass was 82.7±9.2 kg. There were no severe side effects to require exclusion from the study.

No significant differences in demographic and echocardiographic data between the groups were observed at the beginning of the study (Table 1). The average left ventricular mass was 294 g (95% CI, 276-312), and the mean left ventricular mass index was 153 g/m^2 (95% CI, 136-171) for all. There were no significant differences between the groups in left ventricular mass, which ranged from 305 g (95% CI, 250-360) in the group receiving propranolol to 281 g (95% CI, 247-315) in patients receiving chlorthalidone ($p=0.26$). Differences in systolic and diastolic blood pressures between the groups were also not significant, either: systolic pressure ranged from 180.0 mm Hg (nicardipine group) to 187.5 mm Hg (propranolol group) ($p=0.42$), and diastolic blood pressure ranged from 106.8 mm Hg (indapamide and nicardipine groups) to 108.8 mm Hg (propranolol) ($p=0.60$). The same was true for the ventricular performance indexes (Table 1).

Antihypertensive Effects

After a month, a significant decrease in blood pressure was observed in all the groups, with the downward trend continuing until the end of the study (Table 2). Average decrease in systolic pressure for all patients was 12.8%, and 10.4% in diastolic pressure ($p<0.001$). The antihypertensive effect was almost the same in all groups (Table 2). On average, the larg-

Table 1. Baseline values (mean, 95% CI) of parameters measured in 64 patients with left venticular hypertrophy allocated to 4 treatment groups

Parameter[a]	Treatment group				
	indapamide	nicardipine	propranolol	chlorthalidone	p[b]
Sex (women/men)	7/9	8/9	6/9	9/7	0.83
Age (years)	51.2 (46.6-55.8)	52.6 (48.5-56.7)	47.0 (40.1-53.9)	50.8 (45.8-55.8)	0.16
Body weight (kg)	83.6 (79.1-88.1)	82.2 (76.8-87.6)	84.2 (79.5-88.9)	80.8 (75.8-85.8)	0.67
Systolic blood pressure (mm Hg[c])	186.8 (179.0-194.0)	180.0 (173.0-187.0)	187.5 (177.0-198.0)	184.9 (174.0-195.0)	0.42
Diastolic blood pressure (mm Hg)	106.8 (104.0-110.0)	106.8 (104.2-109.2)	108.8 (104.0-113.2)	107.3 (104.1-110.4)	0.60
Heart rate (beats/min)	76.0 (70.2-81.8)	70.1 (65.6-74.6)	76.1 (71.3-80.9)	71.8 (66.3-77.3)	0.27
Romhilt-Estes score[d]	4.6 (4.3-4.9)	4.5 (4.2-4.8)	4.4 (4.1-4.7)	4.4 (4.1-4.7)	0.44
IVSd (mm)	12.8 (11.6-14.0)	11.8 (11.0-12.6)	13.0 (11.4-14.6)	12.7 (11.8-13.6)	0.27
LVPWd (mm)	11.8 (11.1-12.5)	11.2 (10.7-11.7)	12.3 (11.0-13.6)	11.5 (10.8-12.2)	0.18
LVIDd (mm)	51.5 (48.6-54.4)	52.2 (48.9-55.5)	50.0 (47.6-52.4)	48.9 (46.8-51.0)	0.49
LVM (g)	302.7 (270.0-335.0)	289.4 (257.0-322.0)	305.1 (250.0-360.4)	281.0 (247.0-315.2)	0.26
LVMI (g/m2)	153.3 (136.8-170.0)	147.6 (131.0-166.6)	156.3 (130.0-182.5)	147.4 (131.1-164.0)	0.11
LA (mm)	40.5 (38.6-42.4)	38.3 (36.6-40.0)	38.8 (36.4-41.3)	40.5 (38.5-42.5)	0.25
EF (%)	66.6 (62.3-70.9)	68.1 (64.2-72.0)	68.1 (64.8-71.4)	68.5 (65.2-71.8)	0.72
FS (%)	33.9 (31.2-36.6)	34.7 (31.9-37.5)	36.1 (33.7-38.5)	36.6 (34.2-39.0)	0.48
DT (ms)	222.5 (198.0-247.0)	205.3 (182.0-229.0)	223.9 (200.0-248.0)	220.0 (204.0-236.0)	0.41
IVRT (ms)	99.4 (91.3-108.8)	92.9 (85.0-101.0)	101.4 (92.4-110.0)	93.8 (85.4-102.0)	0.23
E/A ratio	0.9 (0.7-1.0)	0.9 (0.8-1.0)	0.9 (0.7-1.1)	0.96 (0.7-1.2)	0.19

[a]IVSd – intraventricular septal thickness at end diastole; LVPWd – posterior wall thickness at end diastole; LVIDd – left ventricular internal dimension at end diastole; LVM – left ventricular mass, calculated as $1.04/(IVSd + LVPWd + LVIDd)^3 - (LVIDd)^3 - 13.6$; LVMI – left ventricular mass indexed by body surface area (>134 g/m^2 in men, and >110 g/m^2 in women); LA – left atrial dimension; EF – ejection fraction; FS – left ventricular shortening fraction; DT – deceleration time; IVRT – isovolumetric relaxation time; E/A ratio – peak E (maximum early LV filling velocity)/peak A (maximum atrial LV filling velocity).
[b]Significance level for Kruskal-Wallis analysis of variance.
[c]1 kPa = 7.5 mm Hg.
[d]According to ref. 17.

Table 2. Changes in systolic and diastolic blood pressure (mean, 95% CI) in 64 hypertensive patients with left venticular hypertrophy during treatment with different antihypertensive drugs

Medication	Blood pressure (mm Hg) after				
	baseline	1 month	3 months	6 months	difference[a] (%)
Indapamide					
systolic blood pressure	186.8 (179.2-194.4)	176.0 (166.9-185.1)	166.9 (158.2-175.6)	165.3 (158.1-172.5)	21.5 (13.6-28.5) (11.5)
diastolic blood pressure	106.9 (103.1-110.7)	98.6 (94.6-102.6)	97.5 (93.8-101.2)	96.8 (93.7-99.9)	10.1 (6.5-13.95) (9.5)
Nicardipine					
systolic blood pressure	180.0 (172.9-187)	169.4 (163.5-175.3)	164.3 (157.7-170.9)	157.7 (152.2-163.2)	22.3 (16.0-28.7) (12.4)
diastolic blood pressure	106.8 (103.8-109.8)	98.2 (94.7-101.8)	99.2 (95.5-102.9)	96.6 (98.9-94.3)	11.0 (6.1 to 14.2) (9.6)
Propranolol					
systolic blood pressure	187.5 (177.4-197.6)	168.5 (161.7-175.3)	161.6 (156.0-167.2)	158.7 (153.3-164.1)	28.8 (18.3-39.4) (15.4)
diastolic blood pressure	108.8 (104.3-113.3)	101.3 (98.1-104.5)	96.4 (92.0-100.9)	94.7 (91.8-97.6)	14.1 (9.3-18.9) (13.0)
Chlorthalidone					
systolic blood pressure	184.9 (174.6-195.2)	172.6 (164.9-180.3)	166.6 (161.2-172.0)	160.3 (157.0-163.6)	24.6 (19.4-29.6) (13.3)
diastolic blood pressure	107.3 (104.3-110.3)	101.7 (99.1-104.3)	97.8 (95.8-99.8)	93.7 (90.8-96.6)	13.6 (9.6-17.5) (12.7)
All patients					
systolic blood pressure	184.1 (175.4-192.8)	171.7 (164.3-179.1)	165.2 (158.5-171.9)	160.5 (154.9-166.1)	23.6 (19.6-27.5) (12.8)
diastolic blood pressure	107.4 (103.9-110.9)	99.9 (96.5-103.3)	97.1 (93.9-100.3)	96.2 (90.2-102.3)	11.2 (9.4-13.0) (10.4)

[a]Difference between the baseline values and values after 6 months of treatment; $p < 0.001$ for all.

est decrease in systolic pressure was recorded in the propranolol group (15.4%), whereas the smallest was noted in the group receiving indapamide (11.5%). The decrease in diastolic pressure ranged from 9.5% in the indapamide group to 13.0% in the propranolol group.

Effect of Antihypertensives on Left Ventricular Wall Thickness and Mass

Left ventricular mass, left ventricular mass index, and left ventricular wall thickness changed from the start to the end of the study (Table 3). Significant left ventricular mass reduction, ranging from 7.9% to 10.1%, was observed in all groups. The average absolute reduction in left ventricular mass at the end of the study was 26.4 g or 8.7%, ranging from 24.2 g (95% CI, -0.6-48.9) in the propranolol group to 29.1 g (95% CI, 13.5-44.7) in the nicardipine group, which is a 7.9-10.1% decrease compared with left ventricular mass 6 months earlier ($p < 0.05$; Fig. 2). In patients treated with indapamide and chlorthalidone, left ventricular mass and left ventricular mass index were more reduced than the left ventricular wall thickness. In patients receiving nicardipine, left ventricular wall thickness and mass parameters decreased significantly. Examinees taking propranolol demonstrated significantly thinner interventricular septum at end diastole (IVSd) and left ventricular posterior wall thickness in diastole (LVPWd), whereas the observed decrease in left ventricular mass and left ventricular mass index was of borderline statistical significance ($p = 0.05$ and $p = 0.06$, respectively; Table 3). The left ventricular internal diameter at end diastole (LVIDd) increased by approximately 2% in the propranolol group, and decreased by 2-3% in other groups, with no significant differences between them (Table 3).

Effects on Heart Performance

Some parameters of left ventricular diastolic function (DT) improved significantly in chlorthalidone and propranolol groups, whereas the parameters of systolic left ventricular function (ejection fraction –

Table 3. Relevant cardiac structural changes (mean; 95% CI) in 64 hypertensive patients with left venticular hypertrophy during treatment with different antihypertensive drugs

Parameter[a]	Parameter value				
	baseline	after 6 months of treatment	% change	decrease[b]	p
Indapamide group					
IVSd (mm)	12.8 (11.6-14.0)	12.3 (11.3-13.3)	3.9	0.5 (0.1-1.1)	>0.05
LVPWd (mm)	11.8 (11.1-12.5)	11.6 (10.9-12.3)	1.7	0.2 (-0.3-0.7)	>0.05
LVM (g)	302.7 (270.0-335.0)	274.6 (241.0-308.0)	9.3	28.1 (12.2-45.0)	0.003
LVMI (g/m2)	153.3 (137.1-170.1)	140.1 (123.1-157.0)	8.6	13.2 (5.2-21.9)	0.006
LVIDd (mm)	51.5 (48.6-54.4)	49.9 (47.4-52.4)	3.1	1.7 (-0.7-4.1)	>0.05
Nicardipine group					
IVSd (mm)	11.8 (11.0-12.6)	11.4 (10.8-12.0)	3.4	0.4 (0.03 to 0.8)	0.05
LVPWd (mm)	11.2 (10.7-11.7)	10.5 (9.9-11.1)	6.2	50.7 (0.4-1.1)	0.001
LVM (g)	289.4 (257.0-322.0)	260.3 (233.1-288.0)	10.1	29.1 (13.5-44.7)	0.001
LVMI (g/m2)	147.6 (131.0-164.2)	133.9 (119.2-149.0)	9.4	13.7 (6.0-21.4)	0.02
LVIDd (mm)	52.2 (48.9-55.5)	51.2 (48.4-54.0)	1.9	1.0 (-0.6-2.6)	>0.05
Propranolol group					
IVSd (mm)	13.0 (11.4-14.6)	12.1 (11.0-133.22)	6.9	0.9 (0.1-1.6)	0.03
LVPWd (mm)	12.3 (11.0-13.6)	11.4 (10.6-12.2)	7.5	0.9 (0.2-1.5)	0.01
LVM (g)	305.1 (250.1-361.0)	280.9 (243.1-318.2)	7.9	24.2 (-0.6-48.9)	0.06
LVMI (g/m2)	156.3 (130.2-182.2)	144.1 (127.0-161.1)	7.8	12.2 (-0.1-24.4)	0.05
LVIDd (mm)	50.0 (47.5-52.5)	51.0 (48.6-53.4)	2.0	-1.0 (-2.4-0.4)	>0.05
Chlorthalidone group					
IVSd (mm)	12.7 (11.8-13.6)	12.6 (11.6-13.6)	0.8	0.1 (-0.4-0.73)	>0.05
LVPWd (mm)	11.5 (10.8-12.2)	11.4 (10.6-12.2)	0.9	0.1 (-0.5-0.6)	>0.05
LVM (g)	281.0 (246.8-315.1)	256.3 (221.2-291.4)	8.8	24.7 (-5.2-53.8)	0.024
LVMI (g/m2)	147.4 (131.0-163.8)	133.9 (118.0-149.8)	9.2	13.5 (-2.8-31.1)	0.024
LVIDd (mm)	48.9 (46.8-51.0)	47.4 (44.7-51.1)	3.1	1.5 (-4.8-3.7)	>0.05
All patients					
IVSd (mm)	12.6±2.3	12.1±1.8	3.9		<0.001
LVPWd (mm)	11.7±1.6	11.2±1.4	4.3		<0.001
LVM (g)	294.4±35.3	268.0±62.2	8.7		<0.001
LVMI (g/m2)	151.0±35.3	137.9±30.5	8.7		<0.001
LVIDd (mm)	50.7±5.2	49.9±5.1	1.6		>0.05

[a]IVSd – intraventricular septal thickness at end diastole; LVPWd – posterior wall thickness at end diastole; LVIDd – left ventricular internal dimension at end diastole; LVM – left ventricular mass, calculated se 1.04/(IVSd+LVPWd+LVIDd)^3 – (LVIDd)^3 – 13.6; LVMI – left ventricular mass indexed by body surface area.
[b]Difference between the baseline values and values after 6 months of treatment.

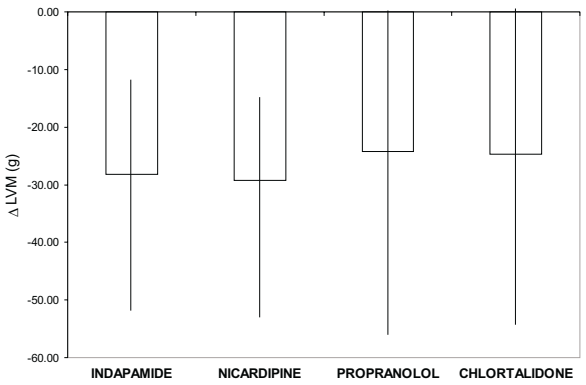

Figure 2. Left ventricular mass changes (ΔLMV), six months after the commencement of therapy in hypertensive patients with left venticular hypertrophy. Bars indicate 95% confidence intervals.

EF and shortening fraction – FS) practically did not change (Table 4). Early and late left ventricular filling velocities and their ratio did not change significantly in any group, although all four groups showed a tendency towards normalization (e.g., increase in E/A ratio).

Correlations between Parameters

There was no significant correlation between blood pressure and left ventricular mass at the beginning of the study. Blood pressures measured continuously over 24 h were significantly lower (20 mm Hg systolic, and 10 mm Hg diastolic) than the office values. Systolic pressures correlated with left ventricular mass index (r=0.54; p=0.011) better than other pressures (Fig. 3). Average 24-h diastolic pressures correlated weakly with left ventricular mass index (r=0.39; p=0.07), but still better than the pressure measured in the office before the study (r=0.25 for systolic, and 0.26 for diastolic pressure; p=0.11).

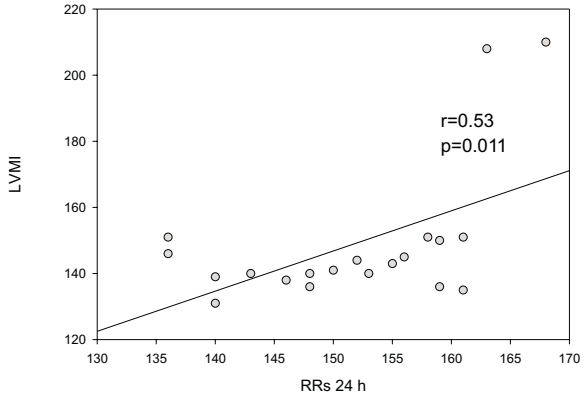

Figure 3. Correlation between left ventricle mass index (LVMI) and average 24 h systolic pressure (RR).

Discussion

The trial results indicated that the effects of the four antihypertensives on arterial blood pressure, left ventricular mass, and left ventricular function in hypertensive patients with left ventricular hypertrophy

Table 4. Relevant functional echocardiographic changes (mean; 95% CI) in 64 hypertensive patients with left venticular hypertrophy during treatment with different antihypertensive drugs

Parameter[a]	Parameter value		
	baseline	after 6 months of treatment	difference[b]
Indapamide group			
LA (mm)	40.5 (38.6-42.4)	40.2 (38.2-42.2)	0.3 (-1.0-1.6)
FS (%)	31.9 (29.2-34.6)	33.1 (31.2-35.0)	1.2 (-0.7-3.2)
EF (%)	66.6 (62.3-70.9)	65.4 (62.4-68.4)	1.2 (-3.1-5.2)
IVRT (ms)	99.4 (70.9-108.0)	92.3 (84.5-100.0)	7.1 (-0.8-14.8)
DT (ms)	222.5 (198.0-247.0)	218.8 (197.0-241.0)	3.7 (-16.5-21.3)
E/A (ratio)	0.86 (0.71-1.01)	1.1 (0.9-1.3)	-0.2 (-0.6-0.1)
Nicardipine group			
LA (mm)	38.3 (36.6-40.0)	38.5 (37.0-40.1)	-0.2 (-1.9-1.5)
FS (%)	34.7 (31.9-37.5)	32.8 (30.9-34.7)	1.9 (0.2-4.1)
EF (%)	68.1 (64.2-72.0)	65.7 (62.4-69.1)	2.4 (0.5-4.3)
IVRT (ms)	92.9 (85.0-101.1)	91.8 (85.2-98.4)	1.1 (-3.2-5.5)
DT (ms)	205.3 (181.7-229.3)	202.9 (182.0-224.0)	2.4 (-7.0-11.7)
E/A (ratio)	0.9 (0.8-1.0)	1.0 (0.8-1.2)	-0.1 (-0.3-0.2)
Propranolol group			
LA (mm)	38.8 (36.6-41.0)	40.3 (38.1-42.5)	1.5 (-3.3-0.4)
FS (%)	36.1 (33.7-38.5)	34.8 (32.8-36.8)	1.3 (-0.8-3.3)
EF (%)	68.1 (64.8-71.4)	67.5 (64.5-70.5)	0.7 (-1.8-3.1)
IVRT (ms)	101.4 (92.4-110)	95.0 (89.2-101.0)	6.4 (-1.5-14.2)
DT (ms)	223.9 (200.0-248.0)	210.4 (191.0-230.0)	13.5 (4.6-21.6)[c]
E/A (ratio)	0.9 (0.7-1.1)	0.9 (0.8-1.0)	0.1 (-0.01-0.1)
Chlorthalidone group			
LA (mm)	40.5 (38.5-42.5)	39.5 (37.4-41.6)	1.0 (-0.7-2.7)
FS (%)	36.6 (34.2-39.0)	35.4 (32.9-37.9)	2.2 (-0.6-4.8)
EF (%)	68.5 (65.2-71.8)	67.1 (63.8-70.4)	1.4 (-3.4-6.1)
IVRT (ms)	93.8 (85.4-102.0)	93.8 (86.6-101.0)	0.02 (-9.0-9.0)
DT (ms)	220.0 (204.0-236.0)	199.7 (188.3-211.0)	20.3 (2.0-40.7)[d]
E/A (ratio)	1.0 (0.6-1.3)	0.9 (0.8-1.1)	0.02 (-0.01-0.1)

[a]LA – left atrial dimension; EF – ejection fraction; FS – left ventricular shortening fraction; DT – deceleration time; IVRT – isovolumetric relaxation time; E/A ratio – peak E (maximum early LV filling velocity)/peak A (maximum atrial LV filling velocity).
[b]Difference between baseline values and values after 6 months of treatment.
[c]$p = 0.04$.
[d]$p = 0.007$.

were comparable. Arterial blood pressure was significantly reduced (approximately by 10-15%) irrespective of antihypertensive medication. After 6 months, systolic and diastolic pressures in all patients decreased on average by 12.8% and 10.4%, respectively, with the decrease in systolic pressure ranging from 11.5% (in the group treated with indapamide) to 15.4% (in the group treated with propranolol), and in diastolic pressure from 9.5% (indapamide) to 13.0% (propranolol). Accordingly, all investigated antihypertensives had equal effect in terms of blood pressure control. Similar results were obtained by other authors (10,13). A meta-analysis of 109 treatment studies showed that mean blood pressure was reduced by 14.9% after some 10 months of treatment (10). Comparing the effects of chlorthalidone (25 mg per day) and propranolol (120 mg per day) after 6 months, a decrease in diastolic pressure by 11% in the upright, and by 14.9% in the supine position was obtained with chlorthalidone, and around 10% in both positions with propranolol (23). In the well-known TOMHS study (13), which compared the effects of five different antihypertensives, arterial pressure was reduced by some 16/12 mm Hg on average, best with chlorthalidone. Similar results were also achieved by administering six different antihypertensives over a year (24). It is interesting to note that in these studies diuretics showed almost the same antihypertensive effect in very low, low, or high doses (e.g., 15, 25 or 100 mg of chlorthalidone per day). Side effects, such as hyperglycemia, hyperuricemia, hyperlipidemia, and hypokalemia, were significantly less expressed when diuretics were given in lower doses (23,25). On the basis of such studies, lower doses of diuretics are being recommended, with 12.5-15 mg of chlorthalidone per day (our patients took 25 mg per day, to the best of our knowledge at the time of planning this study).

Left ventricular mass reduction was almost identical in all four groups of our patients. The absolute decrease in left ventricular mass was 8.7% on average for all patients. Such a decline in left ventricular mass was found in other studies as well: beta-blockers (10,11,13), calcium channel blockers (10,11,13), chlorthalidone (13), and indapamide (14,26) induced a substantial regression in left ventricular mass, in addition to lowering the blood pressure. There are data showing even more pronounced decrease in left ventricular mass, e.g., by 6-16% with indapamide, and by 5-16% with beta blockers, calcium antagonists, and ACE inhibitors (10,11,13). Reports for tiazides and related diuretics are more controversial (0-17% decrease) (12,13). According to earlier studies, diuretics are ineffective in reducing the left ventricular mass, or such effect is too small despite a good pressure control (12). On the other hand, some later studies suggest that diuretics can significantly revert left ventricular mass, even better than other antihypertensives (10,13,24,26). Meta-analysis of 109 treatment studies also showed reduction in left ventricular mass by 12% on average: 15% with ACE inhibitors, 8% with beta blockers and calcium antagonists, and 11% with diuretics (10). ACE inhibitors seemed to be the

best reducers of left ventricular hypertrophy. Activation of the renin-angiotensin system (in addition to increased wall stress due to high blood pressure) is a trophic stimulus promoting cardiac hypertrophy, and its blockade with ACE inhibitors may contribute, independently of blood pressure reduction, to the reversal of myocardial hypertrophy (10). In another study, patients receiving chlorthalidone showed the greatest decrease in left ventricular mass (34 g on average) (13). Thus diuretics, which are mostly recommended as first line drugs, are probably as potent as other antihypertensives in this respect. Additional left ventricular mass decrease in this setting can be ascribed to the reduction (2%) in left ventricular internal diameter at end diastole. Most antihypertensives revert the left ventricular wall thickness, except diuretics, which predominantly shrink left ventricular diameter, while left ventricular wall thinning is less pronounced.

The greatest decrease in left ventricular mass was recorded in our patients treated with nicardipine: by 10.1% on average. A meta-analysis showed that diltiazem and verapamil are more potent than dihidropyridines in reducing left ventricular hypertrophy, probably due to their bradycardic effect (11). Nicardipine, although belonging to dihidropyridines, reduced left ventricular mass by approximately 7% (27,28).

Propranolol abated the left ventricular wall thickness significantly in our patients, but the decrease in left ventricular mass and left ventricular mass index barely reached the margin of statistical significance (Table 3). This could be explained by an increase in the telediastolic left ventricular diameter due to longer diastole, and left ventricular wall thinning. The average decrease in left ventricular mass was smaller in our patients receiving propranolol (24.2 g or 7.9%) than in other groups.

Chlorthalidone and indapamide caused significant reduction in left ventricular mass and left ventricular mass index (by 8.8% and 9.3%, respectively), whereas the left ventricular wall thickness remained almost unchanged, which is partly a result of left ventricular diameter reduction due to relative hypovolemia. These changes are mirroring those observed in the propranolol group. Reduced left ventricular mass caused by chlorthalidone was associated with a reduction in left ventricular wall thickness rather than left ventricular volume (24). These results, ie, harmonious effects on the thickness and diameter, were similar to those from other studies (10,13,26). Decrease in left ventricular internal diameter at end diastole noticed in patients treated with chlorthalidone and indapamide, and increase in left ventricular internal diameter at end diastole in patients receiving propranolol were the expected pharmacological effects of these drugs (13,26). Small changes in left ventricular mass and slight changes in left ventricular diameter in some groups as compared with total could indicate different efficiency of the investigated drugs or insufficient statistical power due to small number of examinees. A recent LIVE study (26) in hypertensive patients with left ventricular hypertrophy demonstrated greater efficacy of indapamide SR 1.5 mg than of enalapril 20 mg in the reduction of left ventricular mass index. Although both drugs equally and significantly reduced blood pressure, indapamide progressively reduced wall thicknesses throughout the one-year treatment period, whereas the effects of enalapril observed at 6 months were not maintained at 12 months. This study (26) supports the earlier findings that diuretics are potent reducers of left ventricular hypertrophy (13,24).

Changes in the maximum early and late transmitral flow velocity, their ratio (E/A), isovolumetric relaxation time, and most other diastolic parameters did not reach statistical significance in any group. Significant improvement was observed in some indices of left ventricular diastolic function only, e.g., left ventricular diastolic function was significantly shortened in propranolol and chlorthalidone groups. Parameters of left ventricular systolic function did not change significantly over the 6-month treatment in any group either. Many studies showed that left ventricular systolic and diastolic function did not change appreciably by pharmacologically reduced left ventricular hypertrophy, e.g., during nicardipine therapy changes in systolic function varied from +12 to -2% (29). With adequate antihypertensive treatment, structural repair of the damaged heart can be achieved sooner and more easily than functional repair (30).

Despite reasonable expectations, there are still no firm proofs that cardiovascular morbidity improves with reversion in left ventricular hypertrophy (13).

Some studies confirmed that the results of ambulatory blood pressure monitoring, especially of average systolic pressures, correlate better with left ventricular mass than occasional office blood pressure measurement (31,32). Correlation coefficients in our study were significantly different. Our results are similar to those of Devereux and Pickering (31) and Verdecchia (32). Hypertensive patients with left ventricular hypertrophy showed higher values and lower oscillations in blood pressure than patients without left ventricular hypertrophy. There was an inverse correlation between the left ventricular mass and degree of overnight reduction in systolic and diastolic pressure (33). Permanent hypertension has the worst prognosis, whereas oscillations, proportionally to the periods of lower pressure, which lower cumulative pressure burden, improve the prognosis. In hypertensive patients with left ventricular hypertrophy, the overnight decrease in blood pressure is absent or less than 10% (33,34), exposing them to a higher risk of stroke (33). The "night dipping" phenomenon prevents or delays development of left ventricular hypertrophy, and antihypertensive drugs may be administered in lower doses in such cases (34).

Cardiovascular complications, including myocardial infarction, stroke, and sudden death, occur more frequently in the morning, between 8 a.m. and noon. Therefore, blood pressure control should be performed in that period. Provided that a patient is acceptably compliant, this is the most important argument for a single administration of long-acting antihy-

pertensives, such as indapamide or chlorthalidone, whose biological half-life exceeds 24 h.

In conclusion, the four investigated drugs achieved almost equal antihypertensive effect, as well as significant and similar reduction in left ventricular mass. Diuretics pronouncedly decreased left ventricular mass in our study, whereas left ventricular wall thickness was reduced only slightly. Reduction in left ventricular mass was not followed by changes in systolic function, and only a few parameters of diastolic function did improve. The ambulatory monitored blood pressures were significantly lower than those obtained in the office, and correlated better with left ventricular mass, particularly average systolic pressures. It seems that systolic pressure elements (e.g. stroke volume and rigidity of large vessels) are more important for left ventricular hypertrophy than diastolic pressure determinants (e.g., heart rate and small vessel resistance).

Most modern antihypertensives, when administered in optimal dosage, reduce the elevated blood pressure to a similar extent, with comparable reversion in left ventricular hypertrophy. The impact of simultaneous reduction in both left ventricular mass and blood pressure upon cardiovascular and total mortality should be further investigated. Presently, the question whether reduction in myocardial mass is more important than decrease in left ventricular wall thickness remains open.

Acknowledgment

We thank the patients who participated in this study. We are grateful to Servier Institute, France, for technical support of this study.

References

1 Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. The Framingham study. Ann Intern Med 1970;72:813-22.

2 Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determinent left ventricular mass in the Framingham heart study. N Engl J Med 1990;322:1561-6.

3 Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345-52.

4 Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. Ann Intern Med 1992;117:831-6.

5 Kannel WB, Castelli WP, McNamara PM, McKee PA, Feinleib M. Role of blood pressure in the development of congestive heart failure. The Framingham study. N Engl J Med 1972;287:781-7.

6 Messerli FH, Ventura HO, Elizardi DJ, Dunn FG, Frohlich ED. Hypertension and sudden death. Increased ventricular ectopic activity in left ventricular hypertrophy. Am J Med 1984;77:18-22.

7 McLenachan JM, Henderson E, Morris KI, Dargie HJ. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. N Engl J Med 1987;317:787-92.

8 Sadler DB, Aurigemma GP, Williams DW, Reda DJ, Materson BJ, Gottdiener JS. Systolic function in hypertensive men with concentric remodeling. Hypertension 1997;30:777-81.

9 Fouad-Tarazi FM. Ventricular diastolic function of the heart in systemic hypertension. Am J Cardiol 1990;65:85G-8G.

10 Dahlof B, Pennert K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients. A meta-analysis of 109 treatment studies. Am J Hypertens 1992;5:95-110.

11 Cruickshank JM, Lewis J, Moore V, Dodd C. Reversibility of left ventricular hypertrophy by differing types of antihypertensive therapy. J Hum Hypertens 1992;6:85-90.

12 Drayer JI, Gardin JM, Weber MA, Aronow WS. Changes in ventricular septal thickness during diuretic therapy of hypertension. Clin Pharmacol Ther 1982;32:283-8.

13 Liebson PR, Grandits GA, Dianzumba S, Prineas RJ, Grimm RH Jr, Neaton JD, et al. Comparison of five antyhipertensive monotherapies and placebo for change in left ventricular mass in patients receiving nutritional-hygienic therapy in the Treatment of Mild Hypertension Study (TOMHS). Circulation 1995;91:698-706.

14 Komajda M, Klimczak K, Boutin B, Brackman F, Guez D, Grosgogeat Y. Effects of indapamide on left ventricular mass and function in systemic hypertension with left ventricular hypertrophy. Am J Cardiol 1990;65:37H-42H.

15 White WB, Schulman P, Karimeddini MK, Smith VE. Regression of left ventricular mass is accompanied by improvement in rapid left ventricular filling following antihypertensive therapy with metoprolol. Am Heart J 1989;117:145-50.

16 Messerli FH. Antihypertensive therapy – going to the heart of the matter. Circulation 1990;81:1128-35.

17 Romhilt DW, Estes EH Jr. A point-score system for the ECG diagnosis of left ventricular hytertrophy. Am Heart J 1968;75:752-8.

18 Rumboldt Z. Antihypertensive drugs [in Croatian]. In: Vrhovac B, editor. Clinical drug evaluation [in Croatian]. Zagreb: Školska knjiga; 1984. p. 327-50.

19 Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977;55:613-8.

20 Devereux RB, Lutas EM, Casale PN, Kligfield P, Eisenberg RR, Hammond IW, et al. Standardization of M-mode echocardiographic left ventricular anatomic measurements. J Am Coll Cardiol 1984;4:1222-30.

21 Brutsaert DL. Diagnosing primary diastolic heart failure. Eur Heart J 2000;21:94-6.

22 Petz B. Basic statistical methods [in Croatian]. Zagreb: JAZU; 1970.

23 Bagatin J, Sardelić S, Pivac N, Polić S, Ljutić D, Rakić D, et al. Comparison of chlorthalidone, propranolol and bopindolol in six-month treatment of arterial hypertension. Int J Clin Pharmacol Res 1998;18:73-8.

24 Gottdiener JS, Reda DJ, Massie BM, Materson BJ, Williams DW, Anderson RJ. Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension. Comparison of six antihypertensive agents. Circulation 1997;95:2007-14.

25 Vardan S, Mehrotra KG, Mookherjee S, Willsey GA, Gens JD, Green DE. Efficacy and reduced metabolic side effects of a 15-mg chlorthalidone formulation in

the treatment of mild hypertension. A multicenter study. JAMA 1987;258:484-8.

26 Gosse P, Sheridan DJ, Zannad F, Dubourg O, Gueret P, Karpov Y, et al. Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study. J Hypertens 2000;18:1465-75.

27 Costantino G, Di Lorenzo L, Buonissimo S, Moccia D, Soro S, Ferrara LA, et al. Echocardiographic analysis of anatomical and functional changes in the left heart ventricle during antihypertensive treatment with nicardipine [in Italian]. G Ital Cardiol 1988;18:644-8.

28 Gosse P, Lacroix P, Roudaut R, Dallocchio M. Left ventricular mass changes with nicardipine therapy in essential hypertension. Cardiovasc Drugs Ther 1989;3: 525-8.

29 Dittrich HC, Adler J, Ong J, Reitman M, Weber M, Ziegler M. Effects of sustained-release nicardipine on regression of left ventricular hypertrophy in systemic hypertension. Am J Cardiol 1992;69:1559-64.

30 Schmieder RE, Messerli FH, Sturgill D, Garavaglia GE, Nunez BD. Cardiac performance after reduction of myocardial hypertrophy. Am J Med 1989;87:22-7.

31 Devereux RB, Pickering TG. Relationship between the level, pattern and variability of ambulatory blood pressure and target organ damage in hypertension. J Hypertens Suppl 1991;9:S34-8.

32 Verdecchia P, Schillaci G, Borgioni C, Gattobigio R, Ambrosio G, Porcellati C. Prevalent influence of systolic over pulse pressure on left ventricular mass in essential hypertension. Eur Heart J 2002;23:658-65.

33 Verdecchia P, Schillacci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, et al. Circardian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990;81:528-36.

34 Littler WA. Sleep and blood pressure: further observations. Am Heart J 1979;97:35-7.

Received: April 3, 2002
Accepted: November 8, 2002

Correspondence to:
Drago Rakić
Department of Internal Medicine
Split University Hospital
Spinčićeva 1
21000 Split, Croatia
drago.rakic@st.hinet.hr