Effects of ACE Inhibitors versus Calcium Antagonists on Left Ventricular Morphology and Function in Patients with Essential Hypertension

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We compared the effects of two long-term antihypertensive treatments (ACE inhibitors vs. Ca antagonists) on left ventricular hypertrophy (LVH) and LV function in patients with essential hypertension and LVH. After a washout period of at least 4 wk, ceronapril or delapril was administered to 18 patients and nifedipine or nicardipine to 15 patients for 6 months. Mean blood pressure (MBP), LV mass (LVM), LV fractional shortening (FS), systolic time intervals (ejection time/pre-ejection period ratio = ET/PEP), and isovolumic relaxation time (IRT) were examined in the pretreatment phase and after 6 months of treatment. MBP and LVM significantly and similarly decreased after treatment in both groups (ACE inhibitors vs. Ca antagonists, ΔMBP: −17.1 ± 1.3 vs. −16.9 ± 1.6%; ΔLVM: −11.7 ± 2.7 vs. −10.0 ± 3.8%, both p = not significant). ACE inhibitors produced significant beneficial changes in FS, ET/PEP, and IRT after treatment as compared with Ca antagonists (ACE inhibitors vs. Ca antagonists, ΔFS: 11.8 ± 3.3 vs. 5.1 ± 4.1%, p < 0.05; ΔET/PEP: 11.9 ± 2.3 vs. 4.7 ± 6.4%, p < 0.05; ΔIRT: −12.0 ± 3.4 vs. −3.8 ± 6.1%, p < 0.05). The results indicate that both ACE inhibitors and Ca antagonists induce significant and similar reductions in blood pressure and LVM in hypertensive patients. ACE inhibitors produce significant improvements in LV function in both systolic and diastolic phases as compared with Ca antagonists. (Hypertens Res 1997; 20: 7–10)

Key Words: hypertension, left ventricular hypertrophy, left ventricular function, Ca antagonists, ACE inhibitors

Recent data from the Framingham cohort have documented that left ventricular hypertrophy (LVH) is an independent and powerful risk factor for congestive heart failure, coronary heart disease, and sudden death (1, 2). Accordingly, it has been suggested that the aim of antihypertensive treatment should be not only to reduce blood pressure to normal but also to reverse LVH in order to reduce cardiovascular complications. Numerous studies have demonstrated that LVH can be reduced by various antihypertensive drugs (3, 4). However, not all antihypertensive drugs are equally effective in reversing LVH. A recent meta-analysis has shown that angiotensin converting enzyme (ACE) inhibitors are the most powerful drugs when given as monotherapy to reduce LVH, closely followed by calcium (Ca) antagonists (4). However, it is still controversial whether the regression of LVH induced by antihypertensive drugs is accompanied by an improvement in LV function. Indeed, clinical studies have reported no consistent improvement in LV function in treated hypertensive patients, despite a significant regression of LVH. In addition, few studies have compared the impact of different antihypertensive drugs on LV function after the reversal of LVH. Therefore, in this study we compared the effects of the two long-term antihypertensive treatments (ACE inhibitors vs. Ca antagonists) on LV structure and function in patients with essential hypertension.

Methods

Study Patients
We enrolled 33 outpatients with essential hypertension who had LVH according to echocardiographic criteria. LVH was defined as M-mode interventricular septal or LV posterior wall thickness of ≥ 10 mm at end-diastole. Patients with any of the following conditions were excluded: secondary hypertension, clinical or electrocardiographic evidence of coronary artery disease, heart failure, atrial fibrillation, renal failure (serum creatinine ≥ 2.0 mg/dl), diabetes mellitus, other severe diseases, or poor compliance with therapy.

Protocol
All hypertensive drugs and other cardiovascular drugs were discontinued for at least 4 weeks. At the end of the washout period, only patients with systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 95 mmHg were included in this study. After this period, the patients were randomly assigned to receive antihypertensive monotherapy.
with either an ACE inhibitor (ceronapril, daily mean dosage 22 mg, range 10-40 mg, n=11 or delapril, 26 mg, 15-30 mg, n = 7) or a Ca antagonist (nifedipine; 27mg, 20-40 mg, n = 10 or nicardipine; 60mg, 30-80 mg, n = 5). The dose of these drugs was increased until optimal blood pressure control was achieved. The evaluations described below were performed at the end of the washout period and after 6 months of treatment.

Methods of Evaluation
Blood pressure
Blood pressure was checked with a regular mercury cuff sphygmomanometer in the sitting position after a 5-min rest. The fifth phase of the Korotkov sounds was taken as the diastolic blood pressure. Two or more readings of blood pressure separated by 2 min were averaged. Heart rate was recorded by palpation of the radial artery for 30 seconds. Mean blood pressure (MBP) was used to evaluate the reduction in blood pressure.

LVH
Echocardiograms were recorded under two-dimensional guidance with an ALOKA SSD 870 instrument equipped with 2.5- or 3.5-MHz transducers, at paper speeds of 50 mm/s and 100 mm/s. The following echocardiographic variables were measured according to the recommendations of the American Society of Echocardiography (5): LV end-systolic dimension and end-diastolic dimension (LVDs and LVDd); and end-diastolic interventricular thickness and LV posterior wall thickness (IVST and LVPWT). Measurements from three cardiac cycles were averaged. These echocardiographic measurements were performed independently by two observers in a random fashion. LVmass (LVM) was calculated according to the formula of Devereux and Reichek (6):

$$LVM (g) = 1.04 \times \left[ \frac{(LVDd + IVST + LVPWT)^3}{LVDd} \right] - 13.6$$

Left ventricular systolic function
LV fractional shortening (FS) was calculated from LVDd and LVDs: $FS \% = \frac{(LVDd-LVDs)}{LVDd} \times 100$. The following variables of systolic time intervals were measured on the basis of simultaneous recordings of the phonocardiogram, external carotid pulse, and electrocardiogram at a paper speed of 100 mm/s: Q-II time was the interval from onset of q wave on the electrocardiogram to onset of the aortic component of the second heart sound; LV ejection time (ET) was the interval from onset of upstroke to dicrotic notch on the carotid pulse tracing, and pre-ejection period (PEP) was calculated by subtracting the ET from the Q-II time. The ratio of ET to PEP was used as an index of LV systolic function. Measurements from at least five consecutive cycles were averaged.

LV diastolic function
LV diastolic function was assessed by measuring isovolumic relaxation time (IRT). IRT was defined as the interval from the second heart sound to mitral valve opening on simultaneous recordings of the echocardiogram and phonocardiogram. Measurements from at least five consecutive cycles were averaged.

Statistical Methods
Results are expressed as mean values ± SEM. Mean values were compared by the paired or unpaired Student’s t test. A p value < 0.05 was considered to indicate statistical significance.

Results
Study Group
Table 1 shows the clinical characteristics of the patients at baseline. There were no significant differences in baseline variables such as age, sex, MBP, HR, and LVM between the two treatment groups.

Effects on Blood Pressure and LVH
In both the ACE inhibitor and Ca antagonist treatment groups, MBP and LVM were significantly reduced after 6 months of treatment as compared with baseline (Table 2). As shown in Table 3, in the ACE inhibitor treatment group, the percent decreases in MBP and LVM relative to baseline were -17.1% and -11.7%, respectively. In contrast, in the Ca antagonist treatment group, the corresponding values were -16.9% and -10.0%, respectively. There were no significant differences in percent changes of MBP reduction and LVM regression after treatment between the ACE inhibitor and Ca antagonist treatment groups.

In both treatment groups, the reductions in LVM were mainly due to decreases in wall thickness, since LV dimensions were unchanged. As compared with baseline, heart rate did not change significantly.
in either treatment group after 6 months.

LV Function
FS and ET to PEP ratio, the indexes of LV systolic function, were significantly increased after 6 months of treatment as compared with baseline in the ACE inhibitor treatment group, but these indexes did not significantly change in the Ca antagonist treatment group (Table 2).

As for LV diastolic function, a significant shortening of IRT was observed in the ACE inhibitor treatment group after 6 months of treatment as compared with baseline. In contrast, IRT was unchanged in the Ca antagonist treatment group.

There were significant differences between the two treatment groups in the percent changes in LV systolic and diastolic function variables, such as FS, ET to PEP ratio, and IRT, relative to baseline (Table 3).

The percent changes in LV systolic and diastolic function variables did not differ significantly between the drugs within each treatment groups, i.e., the ACE inhibitor treatment group (ceronapril vs. delapril) and the Ca antagonist treatment group (nifedipine vs. nicardipine).

Discussion
The present study demonstrated that after 6 months of therapy blood pressure and LVM were significantly reduced by similar extents in both the ACE inhibitor and Ca antagonist treatment groups. In both treatment groups, as previously reported (3, 4), the reductions in LVM were mainly produced by LV wall thinning rather than by a reduction in LV dimension. However, it is of interest that despite the similar decrements in blood pressure and LVM, the two treatment groups differed significantly with respect to LV function after the reversal of LVH. ACE inhibitor treatment induced beneficial changes in LV systolic and diastolic function variables, such as FS, ET to PEP ratio, and IRT, whereas these variables remained unchanged in the Ca antagonist treatment. In general, after the reversal of LVH it is difficult to compare the effects on LV function of different antihypertensive drugs, since LV function may be affected by various factors, such as the severity of hypertensive disease at baseline, duration of treatment, magnitude of blood pressure reduction, and LVH regression. In this study, there were no differences in the initial blood pressure, LVM, age, sex, duration of treatment, and the decrements in blood pressure and LVM between the two treatment groups. The mechanisms responsible for the observed differences between the two treatment groups are unclear, although it has been suggested that besides reducing blood pressure and LVM, non-hemodynamic factors such as the renin-angiotensin-aldosterone system may play an important role in determining LV function after the reversal of LVH.

Experimental studies reported by Weber et al. (7) suggested that the process of LVH in arterial hypertension is characterized by cardiac myocyte growth and by activation of nonmyocyte cells. In particular, disproportionate growth of the nonmyocyte com-
partment (cardiac fibroblasts, vascular smooth muscle, endothelial cells) and accumulation of collagen fibers are the major determinants of pathological LVH, leading to abnormal myocardial stiffness and, ultimately, ventricular dysfunction. The growth of myocytes and nonmyocyte cells are independent of each other. Experimental studies have shown that myocyte growth is most closely influenced by ventricular load, while myocardial fibrosis is related to mineralocorticoid excess rather than hemodynamic factors (8, 9). Brilla et al. (10) demonstrated that the ACE inhibitor lisinopril reduces myocardial fibrosis and improves LV function. In addition, regression of fibrosis was produced by even small doses of lisinopril that did not reduce arterial pressure. Other experimental studies (11) have provided evidence that Ca antagonists of the dihydropyridine type also induce regression of interstitial myocardial fibrosis. Susic et al. (12) showed experimentally that the disparate effects of various antihypertensive agents on ventricular composition and ventricular function after reversal of LVH may depend on differences in the ability to reduce collagen content and concentration. The experimental findings described above support the possibility that the observed disparities in LV function after the reversal of LVH may be derived from differences between ACE inhibitors and Ca antagonists in their ability to reduce myocardial fibrosis. To date, however, no study in humans has confirmed differences among various antihypertensive drugs in their ability to regress myocardial fibrosis.

In the present study, Ca antagonists did not significantly change LV systolic function after 6 months of treatment. Ca antagonists can be expected to have only a modest effect on LV systolic function at rest because an improvement in LV systolic function due to reducing afterload is counterbalanced by the negative inotropic effect of Ca antagonists.

In hypertension, LV diastolic dysfunction is one of the earliest manifestations of LVH. Experimental studies have shown that isovolumic relaxation and early diastolic filling are active processes and are complexly regulated by various factors, including increased afterload (13), the cytosolic calcium content (14), and the presence of LVH (15). Ca antagonists improve impaired LV diastolic function most likely by lowering the blood pressure, decreasing the cytosolic calcium content, and regressing the LVH (16). Indeed, the majority of clinical studies in hypertensive patients have shown that after antihypertensive treatment with Ca antagonists LV diastolic function, as assessed by echocardiography and pulsed Doppler analysis, improves or remains unchanged (17). In this study, Ca antagonists improved the LV diastolic function slightly, but not significantly.

In conclusion, ACE inhibitors and Ca antagonists significantly and to similar extents reduced blood pressure and LVM in patients with essential hypertension. Furthermore, ACE inhibitors induced significant improvements in LV function in both systolic and diastolic phases as compared with Ca antagonists.

References