Aldosterone Antagonist Improves Diastolic Function in Essential Hypertension

Anna M. Grandi, Daniela Imperiale, Rosa Santillo, Elena Barlocco, Andrea Bertolini, Luigina Guasti, Achille Venco

Abstract—Experimental studies demonstrated that mineralocorticoid antagonists prevent or reverse myocardial fibrosis. Therefore, we tested the hypothesis that the aldosterone antagonist canrenone can improve left ventricular diastolic function in essential hypertension. Using digitized M-mode echocardiography and 24-hour blood pressure monitoring (ABPM), we realized a prospective, randomized, controlled study on 34 never-treated essential hypertensives with left ventricular diastolic dysfunction. Echocardiogram and ABPM were repeated after 6 months of effective antihypertensive treatment with ACE inhibitors and calcium antagonists (second evaluation) and then after a 6-month period with 17 patients randomly assigned to add canrenone 50 mg/d to the previous treatment (third evaluation). At the basal evaluation 32 patients had left ventricular concentric hypertrophy, and 2 patients had left ventricular concentric remodeling. All the patients had normal left ventricular systolic function. At the second evaluation blood pressure was reduced ($P<0.0001$), left ventricular mass index decreased ($P<0.0001$), and diastolic function improved ($P<0.0001$). After randomization, the canrenone and control groups had similar 24-hour blood pressure and left ventricular morpho-functional characteristics. At the third evaluation, despite unchanged blood pressure and similar decrease of left ventricular mass index, the canrenone group, compared with control group, showed a significantly greater increase in left ventricular diastolic indices. In essential hypertension, a low dose of aldosterone antagonist added to antihypertensive treatment significantly improved left ventricular diastolic function. This improvement, not accounted for by changes in blood pressure and left ventricular mass, can be therefore ascribed to a direct action of the drug on the myocardium. (Hypertension. 2002;40:647-652.)

Key Words: aldosterone ■ diastole ■ hypertension, essential ■ antihypertensive therapy ■ fibrosis ■ ventricular function, left

Cardiac remodeling in essential hypertension is characterized by myocyte hypertrophy and increased interstitial fibrosis, which results from increased collagen synthesis and unchanged or decreased collagen degradation. The rise in myocardial collagen content plays a major role in the development of left ventricular (LV) diastolic dysfunction by affecting both LV relaxation and stiffness. Experimental studies have demonstrated the central role of aldosterone in promoting cardiac fibrosis, probably through a direct action on the heart mediated by cardiac mineralocorticoid receptors. This profibrotic action, independent of blood pressure (BP) increase, can be effectively opposed by aldosterone-receptor blockade. In experimental studies on rats with renovascular hypertension, hyperaldosteronism, or spontaneous hypertension, the aldosterone antagonist spironolactone was able to prevent or reverse the development of myocardial fibrosis even though the drug did not normalize blood pressure and did not prevent LV hypertrophy.

Therefore, we considered it of interest to test the hypothesis that the aldosterone antagonist canrenone can improve LV diastolic function in patients with essential hypertension. We planned a prospective, randomized, controlled study on never-treated hypertensive patients with LV diastolic dysfunction, defined by means of digitized M-mode echocardiography (see Methods). A significant and stable BP decrease, however obtained, is accompanied by regression of myocardial hypertrophy and often by improvement of LV diastolic function. Therefore, to distinguish the effects of aldosterone antagonist from the effects of BP reduction, we divided the study into 2 parts: during the first part, the patients were treated with antihypertensive drugs to obtain a stable BP decrease for 6 months; during the second part of the study half of the patients were randomly assigned to add canrenone to the previous treatment for 6 months.

Methods

Patients

We enrolled subjects with the following characteristics: essential hypertension (mean 24-hour BP >140 and/or 90 mm Hg), no previous antihypertensive treatment, LV M-mode echocardiogram of good quality and repeatable, presence of LV diastolic dysfunction (peak lengthening rate of LV diameter <3.6 second$^{-1}$ and peak thinning rate of LV posterior wall <8.4 cm/s), normal renal function,
and normal plasma concentrations of electrolytes, renin, and aldosterone. Other criteria of selection were no clinical, electrocardiographic, or echocardiographic evidence of heart failure, myocardial infarction, angina pectoris, congenital or valvular heart diseases, and no systemic diseases, such as diabetes mellitus or connective tissue disorders, which per se could induce changes of LV structure and function. Following these criteria we enrolled 34 patients (21 men, 13 women, mean age 56±6 years, mean body mass index 26.8±3.1 kg/m²).

The patients were judged to have essential hypertension on the basis of history, physical examination, and laboratory findings. The study was approved by the Ethical Committee of the Department of Clinical and Biological Sciences, and all the subjects gave their informed consent.

Study Design

First Part of the Study

After the baseline evaluation (24-hour ambulatory BP monitoring and echocardiographic examination), all the patients began treatment with an ACE inhibitor (enalapril 20 mg/d or ramipril 5 mg/d) and underwent monthly follow-up examinations, with BP measured by mercury sphygmomanometer 3 times, at 10-minute intervals. After the first month, if clinic BP was >140/90 mm Hg, a calcium antagonist was added (amlodipine 5 mg/d or lercanidipine 5 mg/d). At the following visit, if clinic BP was still >140/90 mm Hg, the calcium antagonist was uptitrated to 10 mg/d. At the following control, if clinic BP was still >140/90 mm Hg, hydrochlorothiazide (HCTZ) 12.5 mg/d was added.

After 6 months of stable BP decrease (clinic BP ≤140/90 mm Hg), all the patients underwent the second evaluation (24-hour ambulatory BP monitoring, echocardiographic examination, and blood tests for creatinine and plasma levels of electrolytes, renin, and aldosterone).

Second Part of the Study

Half of the patients were randomly assigned to add canrenone 50 mg/d to the previous therapy, whereas the other 17 patients continued the therapy without changes. Monthly clinic BP and plasma electrolytes were controlled.

After 6 months the patients underwent the third evaluation (24-hour ambulatory BP monitoring, echocardiographic examination, and blood tests for creatinine and plasma levels of electrolytes, renin, and aldosterone).

Noninvasive 24-Hour Ambulatory BP Monitoring

Noninvasive 24-hour ambulatory BP monitoring was performed with an automated Takeda TM 2421; a simultaneous 24-hour heart rate monitoring was obtained. The unit was set to take readings every 15 minutes throughout the 24 hours. We evaluated 24-hour, daytime (7.00 AM to 10.00 PM), and nighttime (10.00 PM to 7.00 AM) systolic and diastolic BP and heart rate.

Echocardiographic Examination

Immediately after the 24-hour BP monitoring, each subject underwent the echocardiographic examination performed using a Hewlett-Packard Sonos 1500 with a 2.0/2.5 MHz transducer. LV M-mode echocardiograms were recorded under two-dimensional control, at a paper speed of 100 mm/s, with a simultaneous ECG. A single operator, not aware of drug treatment and sequence of recordings, digitized 4 consecutive cardiac cycles of each M-mode echocardiogram, using a Numonics 2205 graphic tablet. An IBM personal computer processed digitized data, averaging the 4 cardiac cycles. We evaluated LV end-diastolic diameter, end-diastolic thickness of interventricular septum and LV posterior wall, relative wall thickness, LV mass, peak shortening rate and peak lengthening rate of LV diameter, and peak thinning rate of LV posterior wall. LV mass was normalized for height to the 2.7th power. The normal limits of the parameters in our laboratory have been derived from the evaluation of 200 normal adults. The reproducibility of the echocardiographic measurements have been tested on 20 normal subjects (each examined 3 times by the same ultrasonic technique). The same operator digitized 4 consecutive cardiac cycles of each echocardiogram. The coefficients of variation were as follows: LV end-diastolic diameter 0.4%, septal thickness 3.2%, posterior wall thickness 3.4%, peak shortening rate 1.1%, peak lengthening rate 4.7%, and peak thinning rate 7.3%.

Mitral inflow velocities were evaluated by pulsed-wave Doppler, with the sample volume placed at the tips of mitral leaflets, from the apical 4-chamber view. We measured the ratio between peak early transmural flow velocity (E) and peak late transmural flow velocity (A) (E/A ratio) and the deceleration time of E velocity (DT, time from peak E velocity to the time when E wave descent intercepted the zero line), using the average of 5 beats for the analysis. LV isovolumic relaxation time was measured as the time interval between the aortic closure click and the onset of mitral valve flow using simultaneous registrations of outflow and inflow signals from pulsed-wave Doppler.

Laboratory Measurements

Serum creatinine and potassium were determined using standard methods. Plasma renin concentrations were measured by immunoradiometric assay (Nichols Diagnostics), with a normal range of 5 to 47 mU/L. Plasma aldosterone concentrations were determined by radioimmunoassay (Biochem Immunosystems), with a normal range of 33 to 346 pmol/L.

Statistical Analysis

Statistical analysis consisted of (1) evaluation of BP and LV parameter changes from basal to second to third evaluation in the 34 patients by means of ANOVA for repeated measures, followed by the test of Schéffé. (2) comparison of BP and LV parameter values at second and third evaluation between canrenone and control groups and analysis of treatment effects by means of 2 (between 2 treatment groups) by 2 (repeated measures with 2 levels, at second and at third evaluation) ANOVA, followed by the test of Schéffé. Pearson’s linear correlation coefficient was used for the evaluation of linear correlations between variables. The data were expressed as mean±SD; a probability value <0.05 was considered statistically significant.

Results

Baseline Evaluation

Mean values of BP and LV parameters of the 34 patients are summarized in Tables 1 and 2. LV end-diastolic diameter was normal (<56 mm) in all the patients; 2 patients had LV concentric remodeling (normal LV mass index, relative wall thickness >0.45), 32 patients had LV concentric hypertrophy (LV mass index >50 g/m², men, and >47 g/m², women; relative wall thickness >0.45). All the patients had normal LV systolic function (peak shortening rate of LV diameter >1.9 seconds⁻¹), and, by definition, impaired LV diastolic function (peak lengthening rate of LV diameter <3.6 seconds⁻¹, and peak thinning rate of LV posterior wall <8.4 cm/s).

The first part of the study lasted 7 months for 5 patients who reached the clinic BP goal (clinical BP ≤140/90 mm Hg) after the first month of treatment and lasted 8 to 10 months for the 29 patients who reached the BP goal later. The patients were treated with ACE inhibitor (5 patients), ACE inhibitor and calcium antagonist (24 patients), and ACE inhibitor, calcium antagonist, and HCTZ (5 patients).

Second Evaluation

Body mass index was unchanged and 24-hour BP was decreased in all the patients (Table 1). LV mass index was significantly decreased, because of a reduction in septal and
posterior wall thickness, without changes in LV end-diastolic diameter (Table 2). The index of LV systolic function and all the indices of LV diastolic function improved significantly (Table 2). Serum creatinine and potassium were unchanged; mean plasma renin concentration increased and mean aldosterone concentration decreased (Table 1).

After randomization, the canrenone and control groups did not differ with regard to age, body mass index, 24-hour BP, heart rate, LV morpho-functional characteristics (Tables 3 and 4). Serum creatinine, potassium, plasma renin, and aldosterone concentrations were also not significantly different between the 2 groups (Table 3). The length of the first period (canrenone 8.5±1, control 8.6±1 months, ns) and the drugs used were similar in the 2 groups (ACE inhibitor: canrenone group [3 patients], control group [2 patients]; ACE inhibitor and calcium antagonist: canrenone group [12 patients], control group [12 patients]; ACE inhibitor, calcium antagonist, and HCTZ: canrenone group [2 patients], control group [3 patients]).

**Third Evaluation**

Considering the 34 patients together, at the end of the second 6-month period, body mass index and 24-hour BP were unchanged compared with the second evaluation, whereas mean LV mass index was significantly decreased and LV diastolic parameters improved (Tables 1 and 2). Serum creatinine and potassium were unchanged, and plasma renin and aldosterone concentrations increased (Table 1).

### TABLE 1. Blood Pressure and Heart Rate Parameters in the 34 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal Evaluation</th>
<th>Second Evaluation</th>
<th>Third Evaluation</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.8±3.1</td>
<td>26.8±3.2</td>
<td>26.8±3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Clinic systolic BP, mm Hg</td>
<td>169±18</td>
<td>131±7</td>
<td>130±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinic diastolic BP, mm Hg</td>
<td>102±9</td>
<td>79±7</td>
<td>80±7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP 24-hour, mm Hg</td>
<td>152±16</td>
<td>128±8</td>
<td>126±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP 24-hour, mm Hg</td>
<td>93±15</td>
<td>78±5</td>
<td>76±7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP day, mm Hg</td>
<td>157±16</td>
<td>133±10</td>
<td>131±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP day, mm Hg</td>
<td>99±18</td>
<td>82±6</td>
<td>80±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP night, mm Hg</td>
<td>141±18</td>
<td>121±12</td>
<td>119±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP night, mm Hg</td>
<td>87±18</td>
<td>72±8</td>
<td>71±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart rate 24-hour, beats/min</td>
<td>74±9</td>
<td>73±9</td>
<td>72±8</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate day, beats/min</td>
<td>77±10</td>
<td>77±9</td>
<td>76±10</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate night, beats/min</td>
<td>68±8</td>
<td>65±10</td>
<td>66±8</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>79.4±3.1</td>
<td>81.5±2.9</td>
<td>80.9±3.3</td>
<td>NS</td>
</tr>
<tr>
<td>K⁺, mmol/L</td>
<td>4.3±0.2</td>
<td>4.2±0.1</td>
<td>4.3±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Renin, mU/L</td>
<td>29.3±6.2</td>
<td>53.5±14.6</td>
<td>61.9±15.6†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aldosterone, pmol/L</td>
<td>249.3±38.5</td>
<td>212.7±31.3*</td>
<td>234.6±37.3†</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD.  
*P<0.001 vs basal evaluation; †0.02<P<0.001 vs second evaluation.

### TABLE 2. Left Ventricular Parameters in the 34 Patients

<table>
<thead>
<tr>
<th>LV Parameters</th>
<th>Basal Evaluation</th>
<th>Second Evaluation</th>
<th>Third Evaluation</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial diameter, mm</td>
<td>35±4</td>
<td>35±4</td>
<td>35±4</td>
<td>NS</td>
</tr>
<tr>
<td>LV diastolic diameter, mm</td>
<td>45±4</td>
<td>46±4</td>
<td>45±4</td>
<td>NS</td>
</tr>
<tr>
<td>Septal thickness, mm</td>
<td>13±1.9</td>
<td>11.8±1.6*</td>
<td>11.3±1.2†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Posterior wall thickness, mm</td>
<td>12.5±1.8</td>
<td>11.3±1.4*</td>
<td>10.7±0.9†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.56±0.06</td>
<td>0.50±0.05*</td>
<td>0.47±0.04†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>79.3±22.2</td>
<td>67.3±20.6*</td>
<td>58.5±15.2†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak shortening rate, s⁻¹</td>
<td>2.9±0.8</td>
<td>3.5±0.6*</td>
<td>3.7±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak lengthening rate, s⁻¹</td>
<td>2.9±0.6</td>
<td>4±0.7*</td>
<td>5.1±1.1†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak wall thinning rate, cm/s</td>
<td>6.8±1.2</td>
<td>7.9±1.4*</td>
<td>10.5±1.5†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Isovolumic relaxation time, ms</td>
<td>128±16</td>
<td>96±24*</td>
<td>78±21†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.71±0.19</td>
<td>0.88±0.21*</td>
<td>1.01±0.22†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E-Deceleration time, ms</td>
<td>231±36</td>
<td>209±41*</td>
<td>179±39†</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD.  
*0.005<P<0.001 vs basal evaluation; †0.02<P<0.001 vs second evaluation.
Comparing the canrenone and control groups, 24-hour BP and heart rate, as well as serum creatinine and potassium, were not significantly different between the 2 groups and similar to the second evaluation. Plasma renin and aldosterone concentrations increased significantly only in the canrenone group (Table 3). LV end-diastolic diameter was unchanged in both groups, and LV mass index decreased in both groups, without significant treatment effect (Table 4), ie, the extent of the reduction was similar in the 2 groups (Figure). Peak shortening rate, index of LV systolic function, the extent of the reduction was similar in the 2 groups (Table 4), but percentage changes of both indices from second to third evaluation were significantly greater in canrenone group than in control group (Figure). With regard to the other diastolic indices, E/A ratio increased significantly only in the canrenone group, whereas peak wall thinning rate increased significantly in both groups (Table 4), but percentage changes of both indices from second to third evaluation were significantly greater in canrenone than in control group (Figure). ANOVA (2×2 factors) showed a significant (P<0.005) treatment effect of canrenone for all the diastolic indices. Changes in LV diastolic parameters did not correlate with changes in LV mass index nor with LV mass index or values of diastolic indices at the beginning of the study.

### TABLE 4. LV Parameters in Canrenone Group and Control Group at the Beginning and End of the Second Study Period

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Canrenone Group</th>
<th>Control Group</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Second Evaluation</td>
<td>Third Evaluation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second Evaluation</td>
<td>Third Evaluation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time</td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>LV diastolic diameter, mm</td>
<td>46±4</td>
<td>46±4</td>
<td>NS</td>
</tr>
<tr>
<td>Septal thickness, mm</td>
<td>12.1±1.4</td>
<td>11.6±1.2*</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Wall thickness, mm</td>
<td>11.7±1.5</td>
<td>10.8±1*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.51±0.06</td>
<td>0.47±0.04*</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>65.8±14.6</td>
<td>58.2±12.6*</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Peak shortening rate, s⁻¹</td>
<td>3.5±0.6</td>
<td>3.8±1</td>
<td>NS</td>
</tr>
<tr>
<td>Peak lengthening rate, s⁻¹</td>
<td>3.8±0.6</td>
<td>5.6±1.2†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak thinning rate, cm/s</td>
<td>7.9±1.5</td>
<td>11.5±2‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isovolumic relaxation, ms</td>
<td>98±26</td>
<td>69±21†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.86±0.22</td>
<td>1.11±0.24*</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>E-Deceleration time, ms</td>
<td>209±38</td>
<td>163±34‡</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD.

*P<0.05; †P<0.005; ‡P<0.001 third vs second evaluation; †0.05<P<0.01 third control vs third canrenone.
LV morphology and function, aiming to avoid possible kinds of antihypertensive drugs can exert different effects on half of the patients added a low dose of canrenone to the 140/90 mm Hg for 6 months; during the second period, was designed to obtain a stable BP decrease (clinic BP of BP decrease, we divided the study into 2 periods: the first period showed no changes in serum potassium level in the canrenone group patients, suggesting that combination therapy, with a low dose of aldosterone antagonist added to ACE inhibitor, is safe with regard to serum electrolytes.

During the first period of treatment, ACE inhibitors alone or, in most of the patients, associated with calcium antagonists, induced a stable BP decrease that, in agreement with previous studies, was accompanied by a reduction of myocardial hypertrophy and significant improvement in LV diastolic function. LV systolic function, normal in all the patients at the basal evaluation, increased during treatment, probably because of the concomitant decrease of afterload.

During the second 6-month period of treatment, BP remained unchanged in all the patients, whereas LV mass index showed a further significant decrease, confirming that regression of myocardial hypertrophy is influenced not only by the drugs used and the extent of BP decrease obtained, but also by the length of treatment.

Our main result was with LV diastolic function: the improvement of all diastolic parameters was greater in the canrenone than in the control group, with a significant treatment effect of canrenone. The greater improvement of LV diastolic function in the canrenone group compared with the control group was not accounted for by differences between the 2 groups in BP or LV mass changes, the first remaining unchanged and the second decreasing to the same extent in both groups (the statistical analysis showed no treatment effect of canrenone on changes in LV mass index). It must be underlined also that, at the beginning of the second study period, the canrenone and control groups had similar values for all BP and LV parameters. The hypothesis that changes in cardiac electrolyte levels resulting from diuretic therapy could have a detrimental effect on LV diastolic function, with the effect reversed by treatment in the canrenone group, can be ruled out mainly because of the small number of subjects treated with thiazide diuretics (only 2 patients in the canrenone group and 3 patients in the control group). Moreover, serum levels of potassium were almost identical in the 2 groups.

A recent study of a small number of essential hypertensive patients showed that a low dose of spironolactone added to an ACE inhibitor induced a greater regression of LV hypertrophy than treatment with ACE inhibitor alone, despite similar BP reduction.

This study is not actually comparable to ours for at least 2 reasons. First, the treatment lasted 9 months and we cannot exclude that aldosterone antagonist treatment longer than 6 months can have a greater effect also on LV mass reduction. Second, spironolactone was added to therapy when BP was not controlled, a condition that can enhance the effects of treatment on LV mass.

Discussion

To the best of our knowledge, this is the first study evaluating the influence of aldosterone antagonist on LV diastolic function in patients with essential hypertension. To this aim we selected never-treated, sustained hypertensives (mean 24-hour BP >140 and/or 90 mm Hg) with LV diastolic dysfunction, established by measuring the peak lengthening rate of LV diameter and the peak thinning rate of LV posterior wall, both obtained from digitized M-mode echocardiography. These 2 diastolic parameters, less popular than Doppler-derived indices, have been proven more accurate and specific than Doppler parameters in discriminating between normal and abnormal diastole in patients with myocardial hypertrophy. Moreover, they are far less influenced than Doppler indices by age and heart rate. We evaluated also the more often used Doppler-derived diastolic parameters. Many studies showed that a stable and significant BP reduction is associated with regression of myocardial hypertrophy and improvement of LV diastolic function. Therefore, to distinguish the effects of canrenone treatment from the effects of BP decrease, we divided the study into 2 periods: the first period was designed to obtain a stable BP decrease (clinic BP \( \leq 140/90 \) mm Hg) for 6 months; during the second period, half of the patients added a low dose of canrenone to the previous treatment for another 6 months. Because different kinds of antihypertensive drugs can exert different effects on LV morphology and function, attempting to avoid possible confounding factors, we enrolled never-treated hypertensive patients, and we followed for all the subjects the same drug treatment scheme, beginning with an ACE inhibitor, then adding a calcium antagonist, and subsequently hydrochlorothiazide when needed. Among the nonselective aldosterone receptor antagonists, we chose canrenone because it is the main active metabolite of spironolactone; therefore, it avoids the formation of intermediate products with antiandrogenic and progestational actions, resulting in a greatly decreased incidence of side effects. We used a low dose of canrenone (50 mg/d) hoping to antagonize the cardiac effects of aldosterone without significant additional antihypertensive effects. During the second part of the study, the previous antihypertensive therapy was maintained unchanged in all the patients and BP did not change. This result strongly suggests that canrenone at 50 mg/d did not exert a significant antihypertensive effect, therefore ruling out the possibility that LV changes in the canrenone group were due to an additive antihypertensive action.

Monthly control of electrolytes during the second study period showed no changes in serum potassium level in the canrenone group patients, suggesting that combination therapy, with a low dose of aldosterone antagonist added to ACE inhibitor, is safe with regard to serum electrolytes.

During the first period of treatment, ACE inhibitors alone or, in most of the patients, associated with calcium antagonists, induced a stable BP decrease that, in agreement with previous studies, was accompanied by a reduction of myocardial hypertrophy and significant improvement in LV diastolic function. LV systolic function, normal in all the patients at the basal evaluation, increased during treatment, probably because of the concomitant decrease of afterload.

During the second 6-month period of treatment, BP remained unchanged in all the patients, whereas LV mass index showed a further significant decrease, confirming that regression of myocardial hypertrophy is influenced not only by the drugs used and the extent of BP decrease obtained, but also by the length of treatment.

Our main result was with LV diastolic function: the improvement of all diastolic parameters was greater in the canrenone than in the control group, with a significant treatment effect of canrenone. The greater improvement of LV diastolic function in the canrenone group compared with the control group was not accounted for by differences between the 2 groups in BP or LV mass changes, the first remaining unchanged and the second decreasing to the same extent in both groups (the statistical analysis showed no treatment effect of canrenone on changes in LV mass index). It must be underlined also that, at the beginning of the second study period, the canrenone and control groups had similar values for all BP and LV parameters. The hypothesis that changes in cardiac electrolyte levels resulting from diuretic therapy could have a detrimental effect on LV diastolic function, with the effect reversed by treatment in the canrenone group, can be ruled out mainly because of the small number of subjects treated with thiazide diuretics (only 2 patients in the canrenone group and 3 patients in the control group). Moreover, serum levels of potassium were almost identical in the 2 groups.

A recent study of a small number of essential hypertensive patients showed that a low dose of spironolactone added to an ACE inhibitor induced a greater regression of LV hypertrophy than treatment with ACE inhibitor alone, despite similar BP reduction.

This study is not actually comparable to ours for at least 2 reasons. First, the treatment lasted 9 months and we cannot exclude that aldosterone antagonist treatment longer than 6 months can have a greater effect also on LV mass reduction. Second, spironolactone was added to therapy when BP was not controlled, a condition that can enhance the effects of treatment on LV mass.
Obviously our study does not allow a pathophysiological understanding of the mechanism of action of canrenone; however, the extent of collagen accumulation in the myocardium results from the balance between collagen synthesis and degradation. Therefore, canrenone, inhibiting the aldosterone profibrotic action, could tip the balance toward collagen degradation, obtaining a net reduction of myocardial collagen content.

Our finding that canrenone induces an improvement of diastolic function without a significant effect on LV hypertrophy is in keeping with results of experimental studies demonstrating that aldosterone antagonist is able to oppose the fibrotic effect of aldosterone, normalizing myocardial fibrosis and, therefore, LV diastolic function, without influencing myocardial hypertrophy. Moreover, as recently demonstrated by Brilla and coworkers, the regression of myocardial fibrosis induced by a 6-month treatment with lisinopril was accompanied by improvement of LV diastolic function, without significant regression of LV hypertrophy. All these results clearly demonstrate that myocardial hypertrophy and diastolic dysfunction are partly independent from one another. This conclusion is also supported by the finding of LV diastolic dysfunction in hypertensives with normal LV mass before the development of an echocardiograph.

In conclusion, in patients with essential hypertension, a low dose of aldosterone antagonist added to antihypertensive treatment induced a significant improvement in LV diastolic function. This improvement was not accounted for by BP or LV mass changes different from the control group; therefore, it can be reasonably ascribed to a direct action of the drug on the myocardium.

**Perspectives**

If further larger studies confirm our results, aldosterone antagonists can play a relevant role in the treatment of hypertension. They may also prove beneficial in subjects with a normal renin-aldosterone profile, as low-cost drugs very effective in the normalization of blood pressure and left ventricular changes during antihypertensive treatment: perindopril versus isradipine. J Cardiovasc Pharmacol. 1995;25:737–741.


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