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Long-Term, Dose-Dependent Effects of Spironolactone on Left Ventricular Function and Exercise Tolerance in Patients With Chronic Heart Failure

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OBJECTIVES This study was designed to assess the effects of spironolactone (SP) on left ventricular (LV) function and exercise tolerance in patients with chronic heart failure (CHF).

BACKGROUND In severe heart failure (HF), SP improves survival, but the underlying mechanisms are not clear.

METHODS We randomized 106 outpatients with HF to SP (12.5 to 50 mg/day) (group 1) or control (group 2). Complete echocardiography and cardiopulmonary exercise testing were performed at baseline and 12 months after randomization.

RESULTS Left ventricular end-systolic volume at baseline and at follow-up was 188 ± 94 ml and 171 ± 97 ml in group 1 and 173 ± 71 ml and 168 ± 79 ml in group 2 (treatment group-by-time interaction, $p = 0.03$). Left ventricular ejection fraction at baseline and at follow-up was 33 ± 7% and 36 ± 9% in group 1 and 34 ± 7% and 34 ± 9% in group 2 (treatment group-by-time interaction, $p = 0.02$). At baseline, 9 patients in group 1 and 3 patients in group 2 had a restrictive mitral filling pattern, a marker of severe diastolic dysfunction; at follow-up, 3 patients in group 1 and no patient in group 2 improved their pattern. No patient in group 1 and 4 patients in group 2 worsened their pattern (chi-square, $p = 0.02$). Peak oxygen consumption increased significantly in patients treated with 50 mg of SP and decreased in group 2 (17.7 ± 5.2 vs. 18.5 ± 5.9 and 19.1 ± 5.6 vs. 17.9 ± 5.3, respectively; analysis of variance, $p = 0.01$).

CONCLUSIONS Spironolactone improves LV volumes and function; furthermore, it improves exercise tolerance at the highest administered dose. Our data might explain the mortality reduction during aldosterone antagonism in patients with HF. (J Am Coll Cardiol 2002;40:304–10)

The modulation of neurohormonal activation in patients with chronic heart failure (CHF) is one of the main goals in the management of this condition. It has been shown that the suppression of aldosterone production with angiotensin-converting enzyme (ACE) inhibitors alone is not complete (1); after an initial reduction, aldosterone levels subsequently rise in a variable percent of patients treated with ACE inhibitors (2–4). This brings about important consequences, as aldosterone stimulates collagen synthesis at the myocardial level (5), therefore contributing to the alteration of cardiac structure and function. Furthermore, we have previously shown that elevated levels of aldosterone are associated with impaired exercise tolerance in patients with CHF (6).

The Randomized ALdactone Evaluation Study (RALES) demonstrated a 30% reduction of mortality in New York Heart Association (NYHA) functional class III and IV patients treated with the aldosterone antagonist spironolactone (SP) in addition to standard therapy for CHF (7), but the underlying mechanisms for this are still not clear. No previous randomized study analyzed the effects of aldosterone antagonism on left ventricular (LV) function and exercise capacity in a large population of patients with CHF. Therefore, we aimed to assess whether SP administration might improve LV function and exercise tolerance in patients with CHF already receiving an ACE inhibitor. Finally, we aimed to assess the effects of different doses of SP on the response variables.

METHODS

Patients. Patients were eligible for enrollment if they had a diagnosis of CHF and were in stable clinical condition for at least six months, if they were on an ACE inhibitor at the maximal tolerated dose and had a left ventricular ejection fraction (LVEF) of no more than 45%. In order to obtain an accurate evaluation of diastolic function, only patients in sinus rhythm were included. Treatment with digitalis, diuretics and beta-blockers was allowed, but potassium-

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ANOVA = analysis of variance
CHF = chronic heart failure
E/A = E-wave/A-wave ratio
HF = heart failure
LV = left ventricular
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association
RALES = Randomized ALdactone Evaluation Study
RMFP = restrictive mitral filling pattern
SP = spironolactone
VE = minute ventilation
VCO_2 = carbon dioxide production
VO_2 = oxygen consumption

sparing diuretics were not permitted. Patients were excluded from the study if they had valvular heart disease, unstable angina, recent myocardial infarction (<6 months), active cancer, renal failure (serum creatinine >150 μmol/l), hyperkaliemia (serum potassium >5.0 mEq/l) or hepatic failure. The local ethics committee approved the protocol and every patient gave written informed consent before the beginning of the study.

After an initial clinical evaluation, 106 patients were randomized to SP treatment (n = 54, group 1), at an initial dose of 25 mg once daily or control group (n = 52, group 2) for 12 months. Follow-up evaluation was performed every four weeks and included measurements of serum potassium and creatinine. In the presence of normal potassium and creatinine levels, the SP dose was titrated up to 50 mg once daily. If hyperkaliemia developed, the dose of SP could be adjusted to a minimum of 12.5 mg once daily. Study medication could be withheld in the event of persistent hyperkaliemia after dose adjustment, serum creatinine levels of more than 200 μmol/l or severe breast pain or gynecomastia. At baseline and 12 months after randomization every patient underwent a complete clinical and echocardiographic evaluation, cardiopulmonary exercise testing and assessment of neurohormonal activation. Venous blood samples for hormonal measurements were obtained in a fasting state, between 8 AM and 9 AM, after a 30-min supine rest. The concentrations of aldosterone and renin were measured by a sandwich radioimmunoassay (Biochem Immuno System, Rome, Italy) at the Laboratory of Clinical Chemistry of our hospital. Norepinephrine was measured by high performance liquid chromatography. The reference values in our laboratory are 3.9 to 49.3 mU/l for renin, 215 to 475 pg/ml for norepinephrine and 0.1 to 0.42 nmol/l for aldosterone.

Echocardiography. An echocardiographic evaluation was performed in every patient before randomization and after 12 months of treatment by an operator blind to the treatment group. Left ventricular end-diastolic and end-systolic volumes and ejection fraction were measured from apical four-chamber view using the monoplane area-length method. Left atrial area was measured at end-systole (the largest dimension) from an apical four-chamber view (area-length method). Left atrial volume was calculated from the left atrial area as previously reported (8).

Mitral flow velocities were recorded using an apical four-chamber view, placing a 0.5 to 1.0 cm pulsed-wave Doppler sample volume between the tips of the mitral leaflets, where maximal velocity was recorded. E- and A-wave velocities and their ratio (E/A) and A-wave duration were measured. Deceleration time of the E-wave was measured as the interval from peak early mitral filling to an extrapolation of the deceleration to 0 m/s. A restrictive mitral filling pattern (RMFP), marker of severe diastolic dysfunction (9), was defined as: 1) E/A ratio >2; or 2) E/A ratio >1 and E-wave deceleration time <140 ms. According to the mitral filling pattern at follow-up compared with baseline, three conditions were expected: 1) improvement, if patients with a baseline RMFP had a reversal of the diastolic filling; 2) unchanged RMFP; or 3) newly developed RMFP.

Cardiopulmonary exercise testing. Patients underwent a symptom-limited bicycle ergometer exercise test at a constant cadence of 60 rpm. The test was supervised and interpreted by a physician blind to treatment group. A continuous ramp protocol was used in which work rate was increased by 10 W/min. Gas exchange was monitored during the exercise test with a computerized metabolic cart (SensorMedics, Vmax 229, Yorba Linda, California). Oxygen uptake (VO_2), carbon dioxide production (VCO_2), minute ventilation (VE) and respiratory exchange ratio were measured online every 10 s using a standard inert gas dilution technique. Peak VO_2 was defined as the highest VO_2 achieved during exercise. The slope of the relation between ventilation and carbon dioxide production (VE/VCO_2) was calculated from the exercise data and taken as an index of the ventilatory response to exercise.

Statistical analysis. Data are expressed as mean ± SD. Time-sequence (between baseline and 12-month-follow-up) changes and group comparisons were assessed by repeated measure analysis of variance (ANOVA) models. Additionally, comparisons within group between baseline and 12 month-follow-up were made by Student *t* test for paired data. Categorical data were compared by using a chi-square test. Linear regression analysis was used to determine the relations between variables. Commercially available statistical software was used (Statview 5.0, Abacus Concepts Inc; SAS 6.12, SAS Institute, Cary, North Carolina). A p value <0.05 was considered statistically significant.

RESULTS

A total of 106 patients were enrolled in the study: 54 were assigned to SP treatment and 52 to control group. Of the 106 randomized patients, 13 did not undergo repeat clinical and echocardiographic assessment for the following reasons: 7 patients because of death (3 in group 1, 4 in group 2), 2

Table 1. Clinical Variables of Study Population at Baseline

	Total Population (n = 106)	Control Group (n = 52)	Spironolactone (n = 54)
NYHA functional class	2.2 ± 0.7	2.1 ± 0.7	2.3 ± 0.7
Gender (male/female)	92/14	46/6	46/8
Age (yrs)	62.1 ± 8.3	61.7 ± 9.8	62.5 ± 7.9
Etiology			
Idiopathic n (%)	38 (36)	19 (37)	19 (35)
Ischemic n (%)	68 (64)	33 (63)	35 (65)
BMI (kg/m^2)	26.9 ± 4.1	27.1 ± 4.1	26.8 ± 4.0
S-Sodium (mEq/l)	139 ± 3	139 ± 2	139 ± 3
S-Potassium (mEq/l)	4.3 ± 0.3	4.3 ± 0.4	4.3 ± 0.3
S-Creatinine (μmol/l)	98.7 ± 25.3	100.0 ± 31.1	96.3 ± 19.2
Max. ACE inhibitor dose (%)	62 ± 36	58 ± 36	66 ± 35
Frusemide dose (mg)	47 ± 52	52 ± 36	42 ± 36
Beta-blockers, n (%)	73 (69)	34 (65)	39 (72)

Data are expressed as mean ± SD or number (%).

ACE inhibitor dose = percentage of maximally recommended angiotensin-converting enzyme inhibitor; BMI = body mass index; NYHA = New York Heart Association.

patients in group 2 and 1 patient in group 1 because of worsening HF and prolonged hospitalization and 3 patients because of hyperkaliemia requiring withdrawal of the study medication. The remaining 93 patients completed the 12 month-follow-up evaluation (47 patients in group 1 and 46 patients in group 2).

The mean SP dose was 31.1 ± 15.6 mg/day. Spironolactone was given at a dose of 25 mg/day in 22 patients and was uptitrated to 50 mg/day in 16 patients. In the remaining nine patients a dose of 12.5 mg/day was given. Gynecomastia was observed in two patients, but was well tolerated and therefore the drug administration was not discontinued.

The clinical baseline characteristics of study population are summarized in Table 1. Most patients were men and had CHF of ischemic origin. The percentage of the maximally recommended dose of ACE inhibitor averaged 62 ± 36% in the whole population and 66 ± 35% and 58 ± 36% in group 1 and group 2, respectively (p = NS). The fruosemide dose was 47 ± 52 mg in the whole population and 42 ± 36 mg and 52 ± 36 mg in group 1 and group 2, respectively (p = NS). The frequency of therapy with beta-blockers was 69% and was similar in the two groups of patients (72% vs. 65%, p = NS).

Plasma aldosterone levels at baseline and at follow-up were 0.26 ± 0.1 nmol/l and 0.38 ± 0.5 nmol/l in group 1 and 0.26 ± 0.1 nmol/l and 0.24 ± 0.2 nmol/l in group 2 ($p < 0.05$ for treatment group-by-time interaction); plasma renin levels at baseline and at follow-up were 76.8 ± 86.9 mU/l and 231.7 ± 259.9 mU/l in group 1 and 85.9 ± 110.7 mU/l and 108.7 ± 207.4 mU/l in group 2 (p = 0.0055 for treatment group-by-time interaction). These effects of SP reflect the loss of negative feedback inhibition on the renin-angiotensin system. Plasma norepinephrine levels at baseline and at follow-up were 385 ± 284 pg/ml and 452 ± 194 pg/ml in group 1 and 371 ± 224 pg/ml and 427 ± 223 pg/ml in group 2 (treatment group-by-time interaction, p = NS).

Echocardiography. Baseline and follow-up echocardiographic characteristics of the study population are summarized in Table 2. There was a significant reduction in LV end-systolic volume and a borderline reduction in LV end-diastolic volume in group 1 patients, whereas there were no changes from baseline in group 2 patients (treatment group-by-time interaction, p = 0.03 and p = 0.06, respectively). At follow-up, the left atrial end-systolic volume significantly decreased in group 1 patients compared with baseline (paired *t* test, $p < 0.01$). Left ventricular ejection fraction significantly improved in group 1 and did not change in group 2 (treatment group-by-time interaction, p = 0.02).

Among the mitral flow Doppler parameters, a trend versus improvement was seen for E/A ratio in group 1 patients and no significant changes were observed in group 2 (treatment group-by-time interaction, p = 0.07). At baseline, 9 patients in group 1 and three patients in group 2 had a RMFP; at follow-up, three patients in group 1 and no patients in group 2 improved their pattern; no patients in group 1 and 4 patients in group 2 worsened their pattern (chi-square test, p = 0.02).

Table 2. Echocardiographic Characteristics of Study Population at Baseline and 12 Months After Randomization

	Control Group (n = 46)		Spironolactone (n = 47)		p Value (Repeated-Measures ANOVA)
Variable	Baseline	Follow-Up	Baseline	Follow-Up	
LVEDV (ml)	257 ± 80	253 ± 89	275 ± 104	251 ± 105*	0.06
LVESV (ml)	173 ± 71	168 ± 79	188 ± 94	171 ± 97*	0.03
LVEF (%)	34 ± 7	34 ± 9	33 ± 7	36 ± 9*	0.02
LAmax (ml)	99 ± 34	95 ± 34	102 ± 38	89 ± 36*	NS
E max (m/s)	0.61 ± 0.20	0.62 ± 0.22	0.62 ± 0.21	0.59 ± 0.21	NS
A max (m/s)	0.72 ± 0.22	0.69 ± 0.19	0.65 ± 0.19	0.68 ± 0.18	NS
E/A ratio	1.1 ± 1.3	1.0 ± 0.72	1.2 ± 1.0	0.94 ± 0.64	0.07
DtE (ms)	220 ± 69	214 ± 88	217 ± 93	219 ± 67	NS

Symbols refer to Student *t* test for paired data. *$p < 0.01$ vs. baseline.

A max = mitral A-wave velocity; ANOVA = analysis of variance; DtE = E-wave deceleration time; E max = mitral E-wave velocity; LAmax = left atrial end-systolic volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

Table 3. Exercise Variables of Study Population at Baseline and 12 Months After Randomization

Variable	Control Group (n = 46)		Spironolactone (n = 47)		p Value (Repeated Measures ANOVA)
	Baseline	Follow-Up	Baseline	Follow-Up	
Peak VO_2 (ml/min/kg)	18.5 ± 5.5	17.8 ± 5.3†	16.4 ± 4.8	16.8 ± 4.9	<0.05
Absolute pVO_2 (ml/min)	1503 ± 548	1407 ± 504*	1279 ± 466	1269 ± 466	NS
% Predicted pVO_2	69 ± 18	70 ± 19	63 ± 19	64 ± 18	NS
RR	1.2 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	NS
Exercise time (min)	9.9 ± 2.2	10.0 ± 2.2	9.5 ± 2.1	9.6 ± 2.3	NS
VE/VCO_2 slope	36.5 ± 6.9	35.9 ± 6.0	37.4 ± 7.5	35.1 ± 5.6	NS
Heart rate (beats/min)	76 ± 18	72 ± 13	71 ± 12	72 ± 13	NS
SBP (mm Hg)	137 ± 27	131 ± 24	134 ± 17	128 ± 21	NS
DBP (mm Hg)	88 ± 15	85 ± 11	80 ± 11	81 ± 10	NS

Data are expressed as mean ± SD. Symbols refer to Student *t* test for paired data. *$p < 0.01$ vs. baseline; †$p < 0.001$ vs. baseline.
ANOVA = analysis of variance; DBP = diastolic blood pressure; RR = respiratory gas exchange ratio; SBP = systolic blood pressure; VE/VCO_2 = relation of the minute ventilation to carbon dioxide production; VO_2 = oxygen consumption.

Exercise capacity. Table 3 summarizes the results of the exercise variables at baseline and at follow-up in the two groups of patients. Peak VO_2 significantly decreased in group 2 patients compared with baseline (*t* test for paired data, $p < 0.001$) and did not change in group 1 patients (treatment group-by-time interaction, $p < 0.05$). Absolute peak VO_2 showed similar changes. There was a trend towards a decreased VE/VCO_2 slope in group 1, but this did not reach a statistically significant difference. Exercise time, percent predicted peak VO_2 and respiratory gas exchange ratio did not significantly change in the two groups. The absolute changes of LVEF from baseline showed a significant, but weak, relation with the absolute changes of peak VO_2 from baseline ($p < 0.05$, $r = 0.23$).

Dose-dependent effect of SP. In order to assess whether the SP dose might have an effect on the response variables, we performed an ANOVA analysis and found a dose-dependent effect on LVEF ($p < 0.05$) and peak VO_2 (<0.05), as represented in Figure 1, with the greatest benefits from SP in those patients treated with 50 mg of the drug. The increase in plasma renin levels was highest in the group of patients treated with 50 mg of SP compared with the group of patients treated with a lower dose ($p < 0.05$) (Fig. 1).

DISCUSSION

In the present study we found a significant improvement in LV volumes, systolic function and a trend versus improvement of diastolic function after 12 months of treatment with SP in ambulatory patients with CHF already on standard treatment for this condition. The effect of SP on LV systolic function was dose-dependent, with the greatest benefits in the group treated with 50 mg of the drug. Furthermore, there was a significant improvement in exercise capacity in the group of patients treated with the highest dose of the drug, whereas there was a significant reduction in peak VO_2 in the control group. Our results suggest that SP administration has important beneficial effects also in patients with mild to moderate CHF, particularly at higher doses.

SP and LV function. Failure of aldosterone suppression during ACE inhibitor therapy carries important consequences in patients with CHF. It has been shown that aldosterone is the hormone most closely associated with a poor outcome in this condition (10). Furthermore, the RALES trial has demonstrated a 30% reduction in mortality in patients with severe CHF already receiving an ACE inhibitor (7). There are several mechanisms potentially contributing to the beneficial effects of aldosterone antagonism in patients on standard therapy for CHF. Aldosterone promotes fluid retention (11) and alters electrolyte balance (12); furthermore, it potentiates the effects of catecholamines (13) and determines baroreflex dysfunction (14). Another negative effect of aldosterone is represented by collagen deposition at the myocardial level. The aldosterone receptor is expressed in the myocardium (15), thus representing the prerequisite for local effects of this hormone. Furthermore, it has been shown that aldosterone production is increased in the failing heart (16). These observations might help to explain the effects of aldosterone antagonism in patients with nonischemic dilated cardiomyopathy (17) and ischemic heart disease (18,19). Tsutamoto et al. (17) have shown a positive effect on cardiac remodeling, LV systolic function and mass in a small population of CHF secondary to idiopathic dilated cardiomyopathy treated with a fixed dose of 25 mg of SP for four months. We found similar results in terms of LV volumes and LVEF. Furthermore, we studied the effects of SP administration on diastolic function. We observed an improvement in LV filling pattern only in patients treated with SP, and a worsening of the pattern during follow-up only in the control group patients. When considering the markers of diastolic dysfunction as continuous variables, we found only a borderline effect for the E/A ratio. This might be due to the low number of patients with marked diastolic dysfunction in our population together with the complex mechanisms determining mitral inflow parameters (20), besides diastolic dysfunction (21). We also observed a significant decrease in left atrial volume in the treated group; this also

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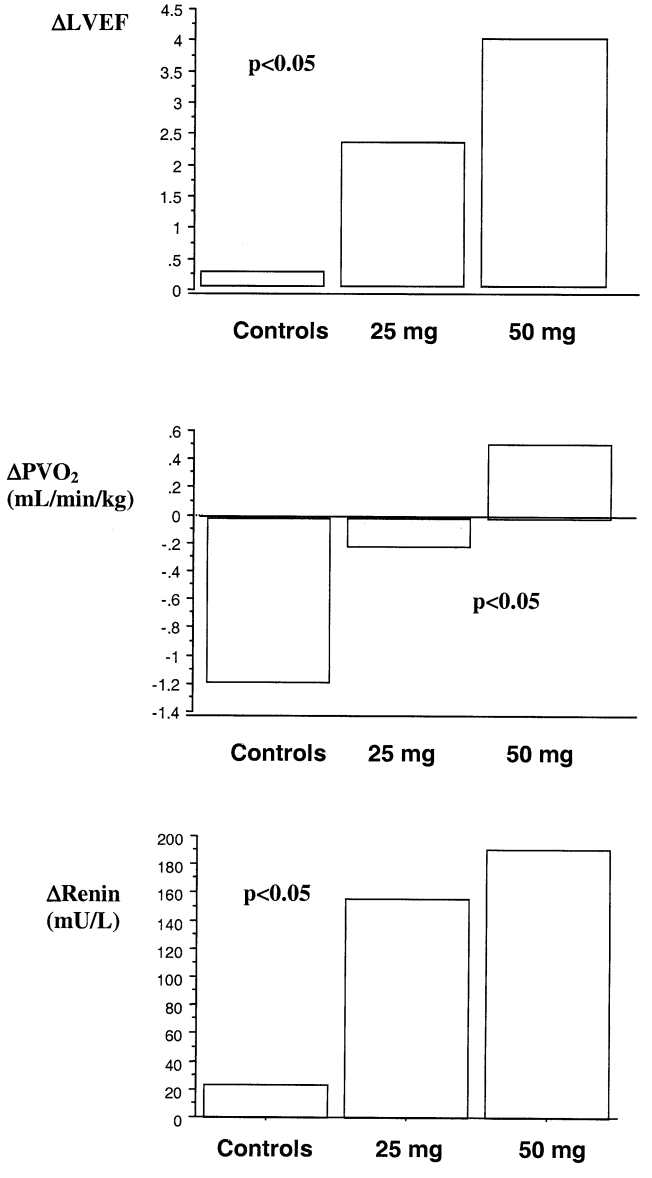

Figure 1. Dose-dependent effects of spironolactone on left ventricular ejection fraction (LVEF), peak oxygen consumption (PVO_2) and plasma renin levels in patients with chronic heart failure treated with 25 mg and 50 mg of the drug and in the control group. Variables are expressed as absolute differences from follow-up and baseline evaluation.

indirectly supports an improvement on LV diastolic function (22).

As the composition of the extracellular matrix is an important determinant of cardiac volumes and mechanics (23,24), the improvement in LV volumes and both systolic and diastolic function might be linked to the reduction in myocardial fibrosis through SP, as previously reported both in animal (25) and human (26,27) studies. A recent paper by Zannad et al. (28) showed a marked reduction in serum levels of markers of cardiac fibrosis in patients treated with SP. Left ventricular systolic and diastolic dysfunction are important prognostic markers in patients with CHF (29–31); therefore, one mechanism leading to the mortality reduction during aldosterone antagonism in CHF might be due to the improvement in LV function.

SP and exercise capacity. The modulation of the neurohormonal activation can improve exercise tolerance in patients with CHF. This has been already demonstrated both for ACE inhibitors, alone or in association with angiotensin II receptor blockers (32,33), and for beta-blockers (34). Thus, in the presence of optimal therapy for CHF, few adjunctive effects from SP would be expected on exercise capacity. Surprisingly, we found a small but significant improvement in peak VO_2 in the group of patients treated with 50 mg of SP. On the other hand, in the control group there was a significant reduction in exercise capacity at follow-up compared with baseline, reflecting the natural history of the disease. This underlines the importance of maximal neurohormonal antagonism at different levels.

The mechanisms underlying these effects of aldosterone antagonism on exercise capacity might be found both in the heart and in the periphery. We found a significant correlation between the absolute changes in LVEF and in peak VO_2 from baseline; nevertheless, there was a wide range of variation, and therefore only a small part of the changes in peak VO_2 can be attributed to central factors. We have previously shown that elevated levels of aldosterone are associated with impaired exercise tolerance and that this effect is not due to the resting hemodynamics (6). Recently, a randomized, placebo-controlled trial on the vascular effects of SP clearly showed a marked improvement in endothelial function and a reduction in angiotensin I/angiotensin II conversion in CHF patients after treatment (35). These effects might also contribute to a better vasodilator capacity during exercise and therefore to an increased exercise tolerance.

Interaction with other drugs. Previous studies on SP in CHF were conducted in patients with standard therapy for this condition, which did not include, at the time of the RALES, the use of beta-blockers in NYHA functional class III and IV patients. In another study (17), only 73% of patients were receiving an ACE inhibitor, and only a small proportion of patients were receiving a beta-blocker; therefore it might be argued that the concomitant use of ACE inhibitors and beta-blockers might blunt the effects of SP. In our study, chronic therapy with ACE inhibitors represented an inclusion criterion and 69% of patients were already treated with beta-blockers at randomization. Therefore, even during optimal therapy for CHF there is enough residual aldosterone production to be blocked by aldosterone receptor antagonism. This is indirectly confirmed by the fact that there was a dose-dependent effect of SP on LV function, exercise capacity and neurohormonal activation.

Study limitations. The present study has several limitations. First, we hypothesize that the effects of SP on LV function might be linked to a reduction in myocardial fibrosis, but we did not measure serum collagen levels; nevertheless, Zannad et al. (28) have demonstrated a significant reduction in serum procollagen type III levels

during aldosterone antagonism. Second, our population does not represent that of the RALES trial, which included patients with severe CHF; consequently, we can only hypothesize that the mortality reduction during SP treatment might be due to an improvement in LV function. On the other hand, in patients with more severe CHF, characterized by a more pronounced neurohormonal activation, the effects of SP on cardiac function might be even more striking. Last, we randomized patients to treatment and to control group. Nevertheless, the absence of the placebo in the present study represents only a minor limitation, because the response variables were objective and have been evaluated by physicians blind to the treatment group.

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