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Aldosterone Receptor Antagonism Induces Reverse Remodeling When Added to Angiotensin Receptor Blockade in Chronic Heart Failure

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Objectives The objective of this study was to determine if adding spironolactone to an angiotensin II receptor blocker improves left ventricular (LV) function, mass, and volumes in chronic heart failure.

Background Add-on spironolactone therapy substantially improves clinical outcomes among patients with severe heart failure (HF) on standard therapy. However, the value of combining spironolactone with an angiotensin II receptor blocker on LV reverse remodeling in mild-to-moderate systolic HF is unclear.

Methods Fifty-one systolic HF patients with left ventricular ejection fraction (LVEF) <40% were randomly assigned to receive 1-year treatment of candesartan and spironolactone (combination group) or candesartan and placebo (control group). Reverse remodeling was assessed by serial cardiac magnetic resonance imaging and echocardiographic tissue Doppler imaging (TDI).

Results There were significant improvements in LVEF (35 ± 3% vs. 26 ± 2%, $p < 0.01$) and reduction of LV end-diastolic volume index (121 ± 16 ml/m^2 vs. 155 ± 14 ml/m^2, $p = 0.001$), end-systolic volume index (88 ± 17 ml/m^2 vs. 120 ± 15 ml/m^2, $p < 0.0005$), and LV mass index (81 ± 6 g/m^2 vs. 93 ± 6 g/m^2, $p = 0.002$) in the combination group at 1 year. In addition, there was significant increase in peak basal systolic velocity and strain by TDI, decrease in index of filling pressure, and increase in cyclic variation integrated backscatter. In the control group, there were no significant changes in all these parameters after 1 year.

Conclusions The addition of spironolactone to candesartan has significant beneficial effects on LV reverse remodeling in patients with mild-to-moderate chronic systolic HF. (J Am Coll Cardiol 2007;50:591–6) © 2007 by the American College of Cardiology Foundation

Excess aldosterone is well known to have diverse deleterious effects in systolic heart failure (HF) patients (1). Previous studies have established the beneficial role of the aldosterone receptor blocker spironolactone in treating patients with severe HF (2), and there is evidence suggesting that aldosterone "breakthrough" occurs that might attenuate the cardioprotective effects of long-term angiotensin-converting enzyme (ACE) inhibitor monotherapy (3,4). Similar concerns regarding aldosterone "breakthrough" with angiotensin II receptor blocker (ARB) monotherapy have been raised, although the results from previous studies are conflicting (5,6). In fact, whether spironolactone might exert an additive beneficial effect to that of ARB on left ventricular (LV) function and reverse remodeling in patients with mild-to-moderate systolic HF is unknown.

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Therefore, we investigated the additive beneficial effects of combining candesartan with spironolactone on reverse LV remodeling with serial cardiac magnetic resonance imaging (CMR) and tissue Doppler imaging (TDI).

Methods

Study protocol and randomization. This was a prospective, randomized, double-blind, placebo-controlled study. Eligible patients with left ventricular ejection fraction (LVEF) <40% and receiving ACE inhibitors more than 6 months were

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ARB = angiotensin II receptor blocker
CMR = cardiac magnetic resonance imaging
CVIB = cyclic variation of integrated backscatter
HF = heart failure
LV = left ventricle/ventricular
LVEDVI = left ventricular end-diastolic volume index
LVEF = left ventricular ejection fraction
LVESVI = left ventricular end-systolic volume index
TDI = tissue Doppler imaging

randomly assigned to replace ACE inhibitors with candesartan 8 mg and spironolactone 25 mg once daily (combination group) or candesartan 8 mg and a matching identical placebo once daily (control group) over a 1-year study period. According to the study protocol, enrolled patients underwent serial CMR, echocardiography, and clinical assessments and laboratory tests (Fig. 1).

Patients. Eligible patients were receiving standard anti-HF treatment except for potassium-sparing diuretics before randomization. Dosages of these background medications except diuretics were not allowed to change after randomization. Patients were excluded if they had significant valvular heart disease; congenital heart disease; any life-threatening disease with limited life expectancy; or standard contraindications for CMR examination, creatinine concentration >200 μmol/l, potassium level >5 mmol/l, and a history of allergy or side-effect with spironolactone. All patients gave written informed consent. The institutional ethics committee approved the study protocol.

CMR. All CMR were performed with a 1.5-T scanner (Sonata, Siemens, Erlangen, Germany). Cine imaging with steady state precession sequence were performed. Raw images were processed by manual outlining of the endocardial and epicardial borders at end-diastolic and end-systolic frames. Analysis of LVEF, left ventricular end-systolic volume index (LVESVI) and left ventricular end-diastolic volume index (LVEDVI), and LV mass indexes by CMR were calculated with Simpson's rule.

TDI and strain imaging by echocardiography. Echocardiograms were performed with a standard ultrasound machine (Vivid 5 and Vivid 7, GE Vingmed, Horten, Norway). The TDI and strain imaging were acquired as previously described (7). Myocardial longitudinal velocity and deformation curves were obtained, and peak systolic velocity (Sm) or strain during the ejection phase as well as early diastolic velocity (Em) were measured. The filling pressure was estimated by the ratio of transmitral early diastolic Doppler velocity (E) to Em measured at the basal septal segment (E/Em) (8).

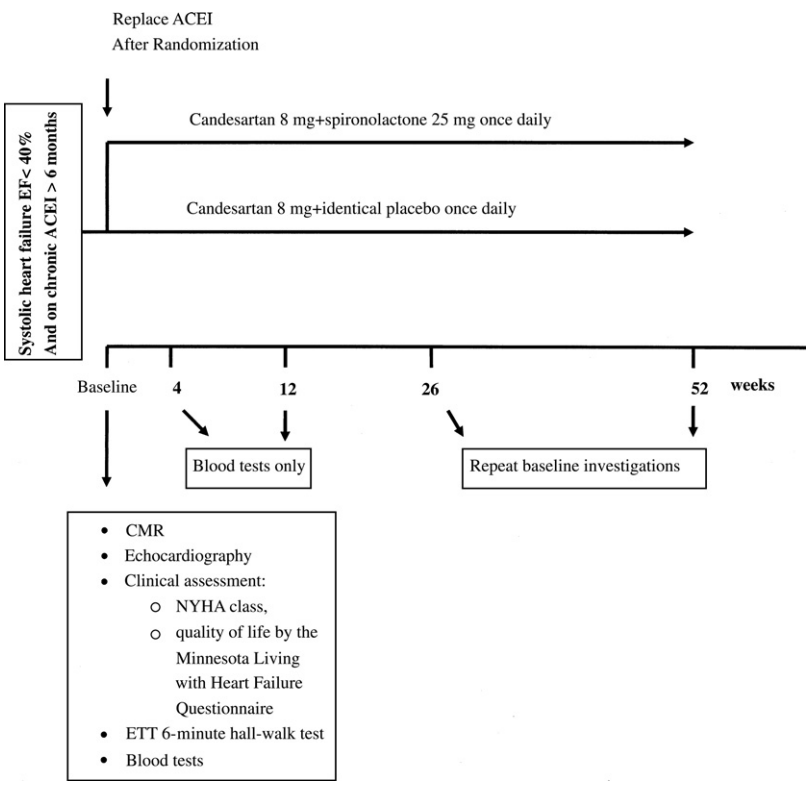

Figure 1 Flow Chart Depicting the Design of the Study

ACEI = angiotensin-converting enzyme inhibition; CMR = cardiac magnetic resonance imaging; EF = ejection fraction; ETT = exercise treadmill time; NYHA = New York Heart Association.

Table 1 Baseline Clinical Characteristics of the Patients

	Candesartan + Spironolactone (n = 23)	Candesartan + Placebo (n = 25)	p Value
Age (yrs)	61.4 ± 12.3	65.0 ± 0.6	0.29
Female/male (%)	3 (13.0)/20 (87.0)	5 (20.0)/20 (80.0)	0.70
Body mass index (kg/m^2)	25.5 ± 2.9	25.3 ± 3.5	0.88
Hypertension (%)	7 (30.4)	10 (40.0)	0.56
History of coronary artery disease (%)	8 (34.8)	11 (44.0)	0.57
Previous myocardial infarction (%)	7 (30.4)	14 (56.0)	0.09
Coronary artery revascularization (%)	4 (17.4)	9 (36.0)	0.20
Hyperlipidemia (%)	13 (56.5)	14 (56.0)	1.0
Diabetes (%)	6 (26.1)	8 (32.0)	0.75
Current cigarette smoking (%)	3 (13.0)	3 (12.0)	1.0
Previous cigarette smoking (%)	12 (52.2)	12 (48.0)	1.0
Primary etiology of HF			
Ischemic heart disease (%)	11 (47.8)	16 (64.0)	0.38
Hypertension (%)	1 (4.3)	2 (8.0)	1.0
Dilated cardiomyopathy (%)	11 (47.8)	7 (28.0)	0.23
Background medications			
Diuretics (%)	11 (47.8)	17 (68.0)	0.24
Beta-blocker (%)	16 (69.6)	18 (72.0)	1.0
Nitrates (%)	14 (60.9)	10 (40.0)	0.25
Aspirin (%)	15 (65.2)	20 (80.0)	0.34
Statins (%)	9 (39.1)	15 (60.0)	0.25
ACEI before randomization (%)	23 (100.0)	25 (100.0)	1.0

All p = NS for intergroup difference at baseline.
ACEI = angiotensin-converting enzyme inhibition; HF = heart failure.

Integrated backscatter imaging. Integrated backscatter imaging was acquired with parasternal long-axis view as previously described (9). The magnitude of cyclic variation of integrated backscatter (CVIB) was defined as the difference between the minimal and maximal values in a cardiac cycle. The final data were presented as mean value of the septum and posterior wall.

Statistical analysis. The study had a 90% power to detect an 8% difference in LVEF and volume with a minimum of 20 subjects in each group with 2-sided alpha of 0.05, assuming an SD of 8% for the CMR measurement of LVEF and LV volumes. All continuous values were expressed as mean ± SE. Comparisons of the baseline characteristics between groups were performed with the Pearson chi-square test for categorical variables. Comparisons within treatment group for CMR volumetric variables at baseline and 26 and 52 weeks were performed by paired *t* test. A repeated measure analysis of variance (ANOVA) for trends were used to assess treatment effect on variables between treatment groups related to volumetric changes and ventricular remodeling. A value of $p < 0.05$ was considered statistically significant. SPSS version 13 was used (SPSS Inc., Chicago, Illinois).

Results

A total of 51 patients were enrolled in the study. Of those, 48 patients were randomized and completed 1 year follow-up. Patients' baseline clinical characteristics are summarized in Table 1. There were no statistically significant differences between the 2 groups in terms of demographic data, etiology of HF, and background medications at baseline and over the course of follow-up period.

Effects on LVEF, volumes, and mass index by CMR. The LVs were dilated at baseline in both groups, indicating severe LV adverse remodeling. There were no significant differences of all baseline CMR parameters between the 2 groups (Table 2). The combination group had significant improvement of LVEF at 26 weeks (Table 3) and further improved at 52 weeks (Table 4). Furthermore, there were significant reductions in LVEDVI, LVESVI, and LV mass index after 1 year of treatment in the combination group (all $p < 0.05$) (Table 4). In fact, the reduction of volume indexes occurred as early as 26 weeks. In contrast, all these parameters were unchanged in the control group (Tables 3 and 4). The intergroup differences for changes in LVEF, LVEDVI, and LVESVI at 52 weeks were statistically significant by repeated measure ANOVA for trends (Fig. 2).

LV long-axis function by TDI. The Sm and basal peak systolic strain increased significantly, and there was a

Table 2 Baseline CMR and Echocardiographic Parameters (Mean ± SEM)

	Candesartan + Spironolactone (n = 23)	Candesartan + Placebo (n = 25)	p Value
CMR at baseline LVEF (%)	26 ± 2	28 ± 2	0.62
LVEDVI (ml/m^2)	154.68 ± 14.21	138.03 ± 10.29	0.34
LVESVI (ml/m^2)	120.30 ± 14.74	101.96 ± 9.42	0.29
LV mass (g)	163.01 ± 11.87	157.31 ± 13.83	0.76
LVMI (g/m^2)	93.22 ± 5.93	91.75 ± 6.74	0.87
Echocardiography at baseline			
E (m/s)	0.77 ± 0.06	0.68 ± 0.05	0.25
A (m/s)	0.81 ± 0.06	0.75 ± 0.04	0.41
E/A	1.08 ± 0.15	1.00 ± 0.15	0.94
IVRT (ms)	110.39 ± 8.65	108.90 ± 5.47	0.88
DT (ms)	216.87 ± 21.81	217.02 ± 15.52	1.0
Sm (cm/s)	3.38 ± 0.16	3.53 ± 0.22	0.6
Em (cm/s)	2.91 ± 0.34	2.93 ± 0.29	0.96
E/Em	33.14 ± 5.25	33.99 ± 0.09	0.94
CVIB (dB)	10.58 ± 0.69	11.80 ± 0.76	0.24
Ts-SD (ms)	42.74 ± 3.44	37.64 ± 3.28	0.29
Systolic strain, basal (%)	12.96 ± 1.00	13.97 ± 1.05	0.49
Systolic strain, mid (%)	9.77 ± 0.76	9.22 ± 1.07	0.67

All p = NS for intergroup difference at baseline.
A = peak atrial inflow velocity; CMR = cardiac magnetic resonance imaging; CVIB = cyclic variation of integrated backscatter; DT = deceleration time; E = peak early diastolic transmitral velocity; E/A = ratio of peak early to late atrial mitral inflow velocities; Em = peak early diastolic myocardial velocity; E/Em = ratio of transmitral E to Em measured at the basal septal segment; IVRT = isovolumic ventricular relaxation time; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; LVMI = left ventricular mass index; Sm = peak systolic velocity; Ts-SD = standard deviation of the time to peak myocardial velocity from 12 segments.

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Table 3 CMR and Echocardiographic Results (Mean ± SEM) at 26 Weeks

	Candesartan + Spironolactone (n = 23)	Candesartan + Placebo (n = 25)
CMR at 26 weeks		
LVEF (%)	31 ± 3*	30 ± 2
LVEDVI (ml/m^2)	130.01 ± 15.13*	136.84 ± 9.49
LVESVI (ml/m^2)	98.32 ± 13.98*	98.76 ± 9.24
LV mass (g)	154.30 ± 12.30	159.72 ± 13.89
LVMI (g/m^2)	87.32 ± 6.16	91.92 ± 6.30
Echocardiography at 26 weeks		
E (m/s)	0.61 ± 0.04†	0.68 ± 0.05
A (m/s)	0.88 ± 0.05	0.88 ± 0.05
E/A	0.73 ± 0.06†	0.89 ± 0.10
IVRT (ms)	122.15 ± 7.67	122.56 ± 5.88
DT (ms)	239.86 ± 16.38	220.58 ± 14.22
Sm (cm/s)	3.86 ± 0.21	3.48 ± 0.20
Em (cm/s)	3.18 ± 0.32	2.99 ± 0.24
E/Em	21.37 ± 0.02†	25.83 ± 0.03
CVIB (dB)	12.93 ± 0.86†	12.50 ± 0.76
Ts-SD (ms)	39.16 ± 3.51	45.51 ± 2.90
Systolic strain, basal (%)	16.60 ± 0.95†	15.14 ± 0.88
Systolic strain, mid (%)	12.35 ± 1.04†	11.02 ± 1.03

All p = NS for intergroup difference at 26 weeks. *p < 0.01 versus baseline; †p < 0.05. Abbreviations as in Table 2.

marked reduction in E/Em only in the combination group (Tables 3 and 4). These echocardiographic parameters were unchanged in the control group.

CVIB. The CVIB increased significantly in the combination group but not in the control group. This suggested a reduction in myocardial fibrosis after 52 weeks of combination therapy (Table 4).

New York Heart Association (NYHA) functional class, quality of life, and 6-min walking test. The quality of life score was improved similarly in both groups. None of the patients had deterioration in NYHA functional class or significant improvement in the 6-min hall-walk test at the end of the study (Table 5). Two patients in the combination group were hospitalized for congestive HF compared with 4 in the placebo group (p = NS), although this study was not powered to investigate the effect on hospital stays or mortality.

Safety and tolerability of candesartan/spironolactone. There were 3 patients prematurely withdrawn from the study; 1 patient in the combination group and 1 patient in the control group had sustained hypotension. After 1 year, the mean systolic blood pressure decreased in the combination group (127 ± 3 mm Hg to 117 ± 3 mm Hg, p < 0.05). One patient in the combination group had hyperkalemia (5.8 mmol/l) leading to withdrawal from study. The mean serum creatinine level increased in the combination group (from 114 ± 23 μmol/l to 138 ± 69 μmol/l, p < 0.05), although none of the patients reached a level that necessitated withdrawal from the study.

Discussion

This clinical study addresses the beneficial role of dual blockade of angiotensin II and aldosterone receptors on the reverse remodeling process in chronic mild-to-moderate systolic HF. We were able to demonstrate that combination therapy of candesartan and spironolactone produced substantial reverse remodeling in HF, despite maximal medical therapy including beta-blocker medications and in predominantly NYHA functional class II patients. Dual blockade achieves a significant reduction in LV size, improvement in overall systolic function, and reversal of LV hypertrophy. The improvement of CVIB might also reflect the reduction of myocardial fibrosis. These beneficial effects are apparent early after initiation of therapy, and further improvement occurred throughout the entire 1-year treatment period irrespective of HF etiology. Our study provides a rationale for the use of this combination therapy in selected HF patients. The potential role of dual blockade in further reduction of hospital stays for HF or mortality needs to be addressed by a larger clinical trial.

We postulate that one of the cardioprotective mechanisms of dual blockade is possibly through reduction of myocardial fibrosis and reverse remodeling (10). The combination therapy of spironolactone and candesartan resulted in reduction of LV volumes and myocardial fibrosis in an animal study (11). In this study, CVIB assessment showed improvement after combination therapy similar to that observed in hypertensive HF and in keeping with the documented antifibrotic action of aldosterone antagonists seen experimentally (12).

Table 4 Echocardiographic and CMR Results (Mean ± SE) at 52 Weeks

	Candesartan + Spironolactone (n = 23)	Candesartan + Placebo (n = 25)
CMR at 52 weeks		
LVEF (%)	35 ± 3*	31 ± 2
LVEDVI (ml/m^2)	121.10 ± 15.76*	135.13 ± 10.60
LVESVI (ml/m^2)	88.14 ± 17.10*	97.51 ± 10.16
LV mass (g)	144.60 ± 13.46†	157.39 ± 8.67
LVMI (g/m^2)	80.96 ± 6.48†	91.69 ± 4.65
Echocardiography at 52 weeks		
E (m/s)	0.62 ± 0.04†	0.64 ± 0.05
A (m/s)	0.85 ± 0.04	0.84 ± 0.05
E/A	0.76 ± 0.06†	0.83 ± 0.09
IVRT (ms)	118.87 ± 6.24	114.56 ± 4.96
DT (ms)	251.89 ± 15.71	249.29 ± 16.14
Sm (cm/s)	4.04 ± 0.31†	3.62 ± 0.20
Em (cm/s)	3.46 ± 0.27	3.13 ± 0.30
E/Em	19.94 ± 0.02*	24.63 ± 0.03
CVIB (dB)	13.38 ± 1.00†	10.90 ± 0.75
Ts-SD (ms)	37.42 ± 3.69	46.71 ± 3.70
Systolic strain, basal (%)	16.10 ± 1.14†	14.98 ± 0.87
Systolic strain, mid (%)	11.34 ± 0.86	11.69 ± 0.76

All p = NS for intergroup difference at 52 weeks. *p < 0.01 versus baseline; †p < 0.05. Abbreviations as in Table 2.

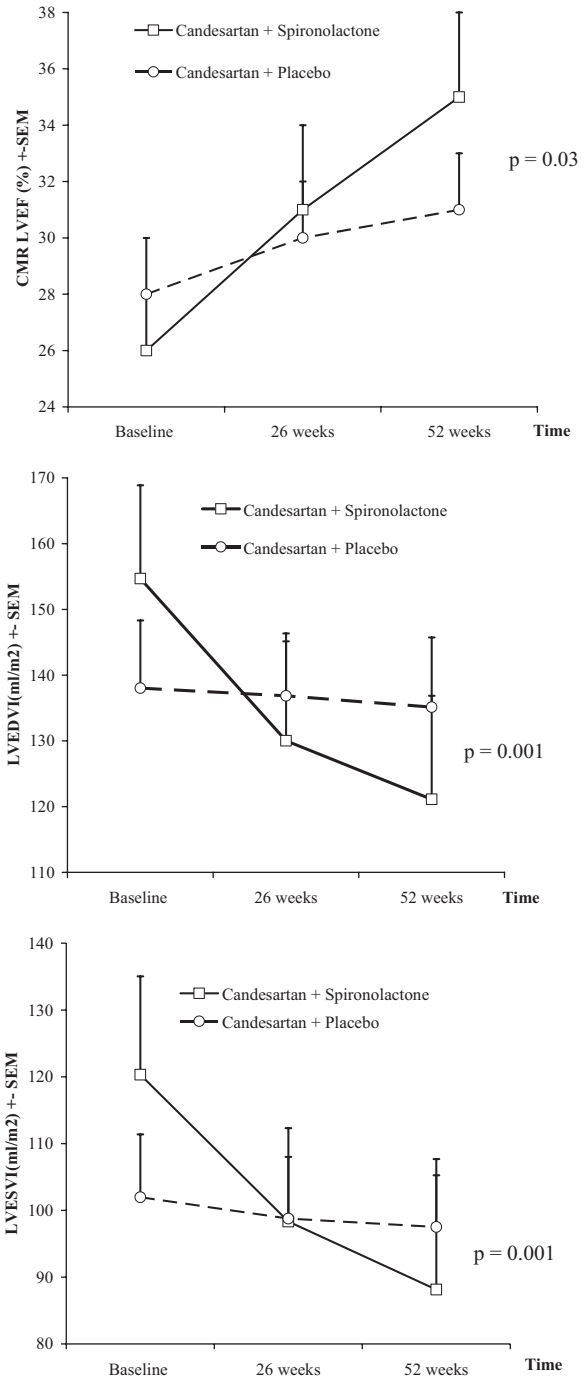

Figure 2 **Serial Changes of LVEF, LVEDVI, and LVESVI by CMR**

CMR = cardiac magnetic resonance imaging; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index.

Another potential beneficial mechanism of combination therapy is more complete inhibition of the renin angiotensin aldosterone system (RAAS). Nonsustained suppression of the RAAS is seen after chronic therapy of beta-blocker (13), ACE inhibitor medications, or ARBs, suggesting that rennin and aldosterone "breakthrough" do occur after the chronic use of current standard anti-HF therapy. Thus, it can be advised that an aldosterone antagonist should be added when an ARB is used alone in treating a patient with systolic HF, because the impact on reverse remodeling is considerable. However, 1 patient (4%) who was taking a combination of an ARB, beta-blocker, and spironolactone developed significant hyperkalemia. Close monitoring of potassium level, careful patient selection, and titration of medication dosage are recommended.

The dose of candesartan used in this study was relatively modest compared with the higher doses used in the CHARM (Candesartan in Heart Failure–Assessment of Mortality and morbidity) trial (14). But in the CHARM study, only about two-thirds of the study population tolerated the target dose of 32 mg because of hypotension and only 24% of patients in the CHARM-Alternative arm were taking spironolactone (15). Lower-dose candesartan has been proven to be efficacious (16). Candesartan 8mg was considered a reasonable therapeutic dose, and we were concerned about the potential risk of hyperkalemia when combining spironolactone with higher doses of candesartan. Of course, our study cannot answer whether spironolactone added to an ARB in larger doses will produce a different result with respect to LV reverse remodeling or the incidence of adverse events. We have provided evidence of a significant beneficial effect on LV reverse remodeling with a relatively low adverse event rate with a low-dose combina-

Table 5 **QOL and ETT Results (Mean ± SE)**

	Candesartan + Spironolactone (n = 23)	Candesartan + Placebo (n = 25)
QOL		
Baseline	23.78 ± 3.34	20.72 ± 2.72
26 weeks	15.09 ± 2.89*	12.54 ± 2.06*
52 weeks	11.86 ± 2.74*	8.71 ± 1.35*
26-week change (%)	−8.86 ± 1.73* (−42.8%)	−7.13 ± 0.44† (−37.1%)
52-week change (%)	−12.30 ± 2.07† (−58.5%)	−10.96 ± 1.91† (−54.0%)
ETT		
Baseline	1,207 ± 61	1,239 ± 48
26 weeks	1,291 ± 56	1,282 ± 41
52 weeks	1,274 ± 58	1,320 ± 48
26-week change (%)	79.95 ± 16.19 (7.19%)	22.46 ± 14.25 (2.38%)‡
52-week change (%)	69.70 ± 14.73 (6.23%)	59.50 ± 17.94 (4.85%)
NYHA		
Baseline, class I (%)	4 (17.4)	3 (12)
Class II (%)	16 (69.6)	18 (72.0)
Class III (%)	3 (13.0)	4 (16.0)
26-week, class I (%)	10 (45.5)	13 (54.2)
Class II (%)	12 (54.5)	10 (41.7)
Class III (%)	0	1 (4.2)
52-week, class I (%)	12 (62.5)	15 (62.5)
Class II (%)	9 (37.5)	9 (37.5)

*$p < 0.05$; †$p < 0.01$ baseline versus 26-/52-week; ‡$p < 0.05$ combination group versus placebo group.

ETT = exercise treadmill time; NYHA = New York Heart Association; QOL = quality of life.

tion therapy in carefully selected patients. The optimal dosage of combining candesartan with spironolactone awaits future studies.

Study limitations. The sample size was relatively small but had adequate power, because we used CMR for volumetric measurements to assess LV reverse remodeling (17). There was a trend in the combination group for lower EF, younger age, less hypertension, coronary artery disease, myocardial infarction, revascularization, more nonischemic etiology, and a 20% less use of diuretic and statin in the combination group, but all these parameters did not reach statistical significance ($p > 0.05$). The positive results achieved in this study were not likely due to fluid overload at baseline, because diuretic dosage was optimized before recruitment and there was no indication to alter diuretic dosages during the study. Furthermore, the changes in LV dimensions and LVEF were used to assess remodeling in this study. Although LVEF might be influenced by transient loading conditions, the dimensional and volumetric changes probably reflect structural modifications occurring in the myocardium. The role of statin therapy on LV remodeling in HF patients is still controversial.

Conclusions

The present study demonstrates that in patients with chronic mild-to-moderate systolic HF, adding spironolactone to an ARB produces incremental beneficial effects on LV reverse remodeling and LV function. Further larger clinical studies are needed to determine whether spironolactone in conjunction with an ARB can reduce mortality or hospital stays for congestive HF.

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REFERENCES

1. Matsumura K, Fujji K, Oniki H, et al. Role of aldosterone in left ventricular hypertrophy in hypertension. Am J Hypertens 2006;19:13–8.
2. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17.
3. Struthers AD. The clinical implications of aldosterone escape in congestive heart failure. Eur J Heart Failure 2004;6:539–45.
4. Sato A, Saruta T. Aldosterone breakthrough during angiotensin-converting enzyme inhibitor therapy. Am J Hypertens 2003;16:781–8.
5. Cohn JN, Anand IS, Latini R, et al., for the Valsartan Heart Failure Trial Investigators. Sustained reduction of aldosterone in response to the angiotensin receptor blocker valsartan in patients with chronic heart failure. Circulation 2003;108:1306–9.
6. Naruse M, Tanabe A, Sato A, et al. Aldosterone breakthrough during angiotensin II receptor antagonist therapy in stroke-prone spontaneously hypertensive rats. Hypertension 2002;40:28–33.
7. Yu CM, Fung JWH, Zhang Q, et al. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. Circulation 2004;110:66–73.
8. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 1997;30:1527–33.
9. Mottram PM, Haluska B, Leano R, et al. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. Circulation 2004;110:558–65.
10. Sanderson JE. New treatments for myocardial fibrosis. Cardiovasc Drugs Ther 2002;16:181–2.
11. Fraccarollo D, Galuppo R, Schmidt I, et al. Additive amelioration of left ventricular remodeling and molecular alterations by combined aldosterone and angiotensin receptor blockade after myocardial infarction. Cardiovasc Res 2005;67:97–105.
12. Brilla CG, Zhou G, Matsubara L, et al. Collagen metabolism in cultured adult rat cardiac fibroblasts: response to angiotensin II and aldosterone. J Mol Cell Cardiol 1994;26:809–20.
13. Fung JW, Yu CM, Yip G, et al. Effect of beta-blockade (carvedilol or metoprolol) on activation of the renin-angiotensin-aldosterone system and natriuretic peptides in chronic heart failure. Am J Cardiol 2003;92:406–10.
14. Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation 2004;110:2618–26.
15. Yusuf S, Pfeffer MA, Swedberg K, et al., for the CHARM Investigators and Committees. Effect of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;363:777–81.
16. Taniguchi I, Kawai M, Date T, et al. Effects of spironolactone during an angiotensin II receptor blocker treatment on the left ventricular mass reduction in hypertensive patients with concentric left ventricular hypertrophy. Circ J 2006;70:995–1000.
17. Bellenger NG, Davies LC, Francis JM, et al. Reduction of sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2000;2:271–8.