Clin. Cardiol. 28, 484–487 (2005)

Spironolactone Improves Diastolic Function in the Elderly

CHANWIT ROONGSRITONG, M.D., PIRAON SUTTHIWAN, M.D., JASON BRADLEY, M.D., JAN SIMONI, D.V.M., SHERRIE POWER, R.N., GARY E. MEYERROSE, M.D.

Division of Cardiology, Texas Tech University Health Sciences Center, Lubbock, Texas, USA

Summary

Background: Diastolic dysfunction is common in the elderly. Increased myocardial fibrosis, a major determinant of diastolic function, has been observed with advancing age. Spironolactone prevents age-related increases in myocardial fibrosis in old normotensive rats.

Hypothesis: Spironolactone, via its antifibrotic activity, can improve diastolic function in the elderly with isolated diastolic dysfunction.

Methods: The study was a prospective, double-blind, randomized, placebo-controlled trial. Thirty elderly subjects between 60 and 85 years of age with isolated diastolic dysfunction and no contraindications for spironolactone were randomized to 25 mg/day of spironolactone or placebo for 4 months. Mitral E/A and deceleration time, plasma levels of carboxy-terminal of procollagen type I (PICP), and brain natriuretic peptide (BNP) were measured at baseline and at the end of 4 months. Plasma level of potassium was also monitored to prevent clinically significant hyperkalemia.

Results: There was no serious adverse event or clinically significant hyperkalemia in the spironolactone group. Compared with baseline values, spironolactone significantly improved mitral E/A ratio (0.71 ± 0.08 vs. 0.84 ± 0.19, $p = 0.025$) and deceleration time (285.5 ± 73.1 vs. 230.0 ± 54.7, $p = 0.035$). There were no significant differences in the magnitude of change in the levels of PICP and BNP between the two treatment groups.

Conclusion: Spironolactone may improve diastolic function in the elderly.

Key words: diastolic function, aging, spironolactone, fibrosis, clinical trial

Introduction

Heart failure is a common cardiovascular disorder in the elderly,[1, 2] occurring in about 6 to 10% of persons aged >65 years.[2] Among age-related alterations of cardiac structure and function, impairment of ventricular diastolic function is, in fact, the most pronounced.[3] With advancing age, diffuse foci of fibrosis due to increased interstitial collagen accumulation are seen in the myocardium.[3] Cardiac fibrosis is a major determinant of diastolic and systolic function of the heart.[4] Aldosterone has been shown consistently to promote cardiac fibrosis in various experimental models.[5, 6] It enhances extracellular matrix and collagen deposition via its direct effect on mineralocorticoid receptors within the myocardium, independent of its effect on blood pressure.[7]

Spironolactone has been shown to prevent cardiac fibrosis in animals even at a dose that has no effect on blood pressure (BP).[8–10] In old normotensive rats, age-induced increases in cardiac extracellular matrix accumulation can be prevented by spironolactone, whereas angiotensin-converting enzyme inhibition (ACEI) has no effect.[11] We hypothesized that spironolactone can prevent the progressive cardiac fibrosis associated with aging and consequently prevent or delay age-related decline in diastolic function in the elderly.

Methods

The study was a prospective, double-blind, randomized, placebo-controlled trial. Thirty subjects between 60 and 85 years of age with evidence of mild diastolic dysfunction on Doppler echocardiography were enrolled from our outpatient

This study is supported by a grant from the Institute of Healthy Aging at Texas Tech University Health Sciences Center, Lubbock, Texas.

Requests for reprints:

Chanwit Roongsritong, M.D.
Division of Cardiology
Texas Tech University HSC
3601, 4th Street
Lubbock, TX 79430-9410, USA
e-mail: chanwit.roongsritong@ttuhsc.edu

Received: May 23, 2005
Accepted with revision: July 15, 2005

cardiology clinic. Subjects with the following criteria were excluded from the study: left ventricular systolic dysfunction (ejection fraction < 45%), serum potassium ≥ 5.5 mEq/l, serum creatinine ≥ 2.5 mg/dl, active myocardial ischemia, uncontrolled hypertension, required long-term steroid use, and history of allergy to spironolactone. The study protocol was approved by the institutional review board at Texas Tech University Health Sciences Center in Lubbock.

After providing informed consent, each subject underwent comprehensive clinical evaluation for signs and symptoms of heart failure. The subjects were then randomized to receive either 25 mg/day of spironolactone or placebo for 4 months and were followed in the cardiology clinic at 2 weeks, 6 weeks, and 4 months. Echocardiography with Doppler was repeated at the end of 4 months. Blood samples were drawn at baseline and at the end of 4 months for measurements of brain natriuretic peptide (BNP) and procollagen type I carboxy-terminal peptide (PICP), a marker of fibrosis. In addition, blood samples were also drawn at 2 weeks for serum potassium. If hyperkalemia (serum potassium > 5.5 mEq/l) developed in the presence of concomitant potassium supplement, the supplement was discontinued and serum potassium was then repeated. Subjects with persistent or clinically significant hyperkalemia, or hyperkalemia in the absence of potassium supplement, were removed from the study.

All blood samples were immediately centrifuged at 1,900 rpm, then stored at −70°C. The PICP levels were determined by commercially available kits from Takara Bio Incorporation, Madison, Wisc., USA. Plasma BNP levels were determined by triage B-type natriuretic peptide assay (Biosite Diagnostics, La Jolla, Calif., USA).

Echocardiographic Studies

Two-dimensional echocardiography with Doppler was performed according to standard guidelines. Transmitral Doppler inflow was recorded in the apical four-chamber view with sampling volume at the levels of the tip of the mitral leaflets. Pulmonary venous Doppler was also recorded in the apical four-chamber view whenever possible. Measurements of mitral inflow deceleration time (DT), early-to-late (E/A) mitral flow velocity ratio, and pulmonary venous systolic to diastolic velocity ratio were performed on three consecutive beats. The averaged values were used for analyses. All of the measurements were performed by the same investigator (PS) who was blinded to the treatment and serum potassium levels. Diastolic dysfunction was diagnosed when the mitral E/A < 1 and DT > 240 ms.

Statistical Analysis

Data are presented as mean ± standard deviation. A Student *t*-test was used for continuous variables and the chi square test was used for categorical variables. A paired Student *t*-test was used for comparison between baseline and follow-up. A p value < 0.05 was considered statistically significant.

Results

A total of 28 subjects completed the study. Two subjects withdrew from the study for nonmedical reasons. Table I illustrates selected demographic data of the study participants. There were no significant differences between the two groups in the baseline characteristics. The majority of the subjects had hypertension and left ventricular hypertrophy. Coronary artery disease was present in about 40% of the subjects. One of the ACEIs or angiotensin receptor blockers (ARBs) at the time of randomization was used in approximately half of the subjects in either group. There were no significant adverse events or clinically significant hyperkalemia during the entire study period.

Effects of Spironolactone on Blood Pressure and Heart Rate

There were no significant differences in baseline BP and heart rate between the two groups (Table II). Systolic BP increased slightly from 142 ± 21 to 144 ± 20 mmHg in the placebo group, whereas it decreased from 144 ± 22 to 138 ±15 mmHg in the spironolactone group. Similar changes were observed with diastolic BP but none of these changes was statistically significant. Furthermore, heart rate at the end of 4 months also did not change significantly from baseline in both groups.

Effects of Spironolactone on Diastolic Function

There were no significant differences in baseline mitral E/A and DT between the two groups (Table III). The follow-up mi-

TABLE I Baseline demographic and echocardiographic data

Variable	Spironolactone	Placebo
Age (years)	71.0 ± 5.5	72.1 ± 6.9
Female (%)	78	78
Hypertension (%)	85	78
Left ventricular hypertrophy (%)	64	50
Coronary artery disease (%)	42	38
ACEI or ARB (%)	47	54
LVEF (%)	64.2 ± 4.9	67.4 ± 3.3
LVEDD (mm)	42.8 ± 6.8	41.9 ± 8.9
Mitral E/A	0.71 ± 0.08	0.68 ± 0.17
Deceleration time (ms)	285.5 ± 73.1	296.9 ± 46.6
Mitral regurgitation		
Mild (%)	27	33
Moderate (%)	7	7
Tricuspid regurgitation		
Mild (%)	33	40
Moderate (%)	13	13

P = not significant for all variables.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic dimension.

TABLE II Effects of spironolactone on blood pressure and heart rate

Variables	Spironolactone	Placebo
Baseline		
SBP (mmHg)	144 ± 22	142 ± 21
DBP (mmHg)	75 ± 14	72 ± 11
HR (beats/min)	77 ± 16	73 ± 10
Follow-up		
SBP (mmHg)	138 ± 15	144 ± 20
DBP (mmHg)	73 ± 14	74 ± 11
HR (beats/min)	77 ± 11	69 ± 7

P = not significant for all variables.
Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate.

tral E/A was slightly but not significantly higher in the spironolactone than in the placebo group (p = 0.17) (Fig. 1). There was a trend toward lower DT in the spironolactone group at follow-up, but the difference did not reach a statistically significant level (p = 0.06).

Compared with baseline values, mitral E/A improved significantly in the spironolactone group (p = 0.025) whereas no significant change was seen in the placebo group (p = 0.75). Similarly, a significant change in DT from the baseline value was only observed in the spironolactone group (p = 0.035).

The plasma levels of BNP were comparable between the two treatment groups at baseline (Table III). Brain natriuretic peptide levels increased slightly in both groups. The magnitude of change appeared higher in the placebo than the spironolactone group (41.0 ± 86.1 vs. 17.8 ± 41.8 pg/ml), but the difference was not statistically significant (p = 0.43).

Effects of Spironolactone on Serum Marker of Cardiac Fibrosis

Baseline levels of PICP were comparable between the two groups (Table III). After 4 months of treatment, PICP levels decreased significantly from baseline in both groups (p < 0.05). However, PICP levels at 4 months were not significantly different between the spironolactone and placebo groups.

TABLE III Effects of spironolactone on indices of diastolic function and plasma levels of carboxy-terminal of procollagen type I (PICP)

Variables	Baseline	Follow-up	Placebo
Mitral E/A ratio			
Spironolactone	0.71 ± 0.08	0.84 ± 0.19	0.025
Placebo	0.68 ± 0.17	0.71 ± 0.29	NS
Deceleration time (ms)			
Spironolactone	285.5 ± 73.1	230.0 ± 54.7	0.035
Placebo	296.9 ± 46.7	305.4 ± 123.8	NS
BNP (pg/ml)			
Spironolactone	54.9 ± 64.2	64.2 ± 49.5	NS
Placebo	51.1 ± 52.7	88.2 ± 93.8	NS
PICP (ng/ml)			
Spironolactone	289.2 ± 59.5	239.3 ± 57.7	<0.05
Placebo	297.6 ± 67.9	236.6 ± 85.8	<0.05

Abbreviations: NS = not significant (> 0.05), BNP = brain natriuretic peptide.

Discussion

To the best of our knowledge, the present study is the first to evaluate specifically the potential benefit of spironolactone in the elderly with isolated diastolic dysfunction. Our study suggests that 4-month treatment with a low dose (25 mg/day) of spironolactone may improve diastolic function in this population.

Spironolactone has previously been shown to improve diastolic function in hypertensive subjects with left ventricular hypertrophy.[12] It has also been recently shown to improve systolic performance in hypertensives with diastolic heart failure.[13] The subjects included in these studies were relatively young, with a mean age of 53 ± 3 years in the study by Sato *et al.*[12] and 62 ± 6 years in the study by Mottram *et al.*[13] Although hypertension was present in the majority of our subjects, almost half of them did not have left ventricular hypertrophy. Since hypertension is quite prevalent in the elderly,[14] excluding patients with hypertension from our study would have significantly limited potential subjects, and the result

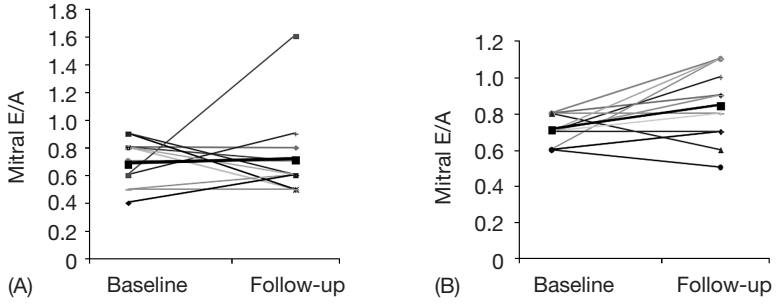

FIG. 1 Baseline and follow-up mitral E/A ratio in placebo (A) and spironolactone group (B). P = 0.75 for placebo and p = 0.025 for spironolactone group.

from such a study design may not be applicable to a significant portion of the elderly population. Moreover, age-related increase in cardiac fibrosis has been observed in the absence of hypertension.[3, 11]

In contrast to our findings on the effect of spironolactone on echocardiographic indices of diastolic function, we were unable to demonstrate a beneficial effect of spironolactone on BNP levels (Table II). The duration of treatment in this study is relatively short, but 4 months of spironolactone has previously been shown to decrease BNP levels in patients with systolic heart failure.[15] Clinical heart failure was not required for enrollment into this study, and all of the subjects had only mild diastolic dysfunction. These two factors may be in part responsible for the normal baseline levels of BNP (< 100 pg/ml) in our study population and limited our ability to detect the effect of spironolactone on BNP. Future study in subjects with more advanced diastolic dysfunction, particularly those with clinical heart failure may yield more favorable results on the effect of spironolactone on BNP levels.

Elevated PICP level (≥ 127 ng/ml) has been shown to correlate with severe fibrosis assessed by myocardial biopsy in hypertensive heart disease.[16] Higher levels of PICP were recently reported in hypertensives with than in those without heart failure.[17] Markedly elevated baseline PICP levels in our study indicated that significant fibrosis was present in our elderly with diastolic dysfunction. After 4 months of treatment with spironolactone, PICP levels decreased significantly from baseline values. A similar finding on the effect of spironolactone on serum markers of cardiac fibrosis has been previously demonstrated in patients with severe systolic heart failure;[18] however, PICP also decreased to the same extent in our placebo group. The explanation for this finding is unclear at this time, but the relatively long storage duration of plasma samples prior to the measurements of PICP at the end of the study (average between 4–6 months) may have partly contributed to the above findings.

Concomitant usage of ACEI or ARB was present in approximately half of our subjects. Spironolactone has, however, been shown to be either superior or additive to ACEIs in reducing cardiac fibrosis.[12, 17] The result of this study suggests that low-dose spironolactone in the presence of ACEIs or ARBs is probably beneficial and safe in the elderly.

Our study is, however, limited by its small sample size and only mild diastolic dysfunction subjects were enrolled. The mitral E/A utilized in this study is dependent on loading condition and other Doppler indices of diastolic function such as tissue Doppler of the mitral valve annulus; it is probably preferable to assess the effect of spironolactone on diastolic function. Finally, the mechanism responsible for the observed benefit of spironolactone in our subjects remains unclear. Although the changes of blood pressure after 4 months of spironolactone did not reach statistical significance, we could not exclude the potential role of hemodynamic effects on our findings.

Conclusion

We found that 4 months of low-dose spironolactone may improve diastolic function in the elderly. Further study evaluating the effect of an aldosterone antagonist on clinical outcomes in the elderly with diastolic heart failure is warranted.

References

1. Kannel WB, Belanger AJ: Epidemiology of heart failure: *Am Heart J* 1991; 121: 951–957
2. Kannel WB: Epidemiology and prevention of cardiac failure: Framingham Study insights. *Eur Heart J* 1987;8(suppl F):23–26
3. Kitzman DW: Diastolic function in the elderly, genesis and diagnostic and therapeutic implications. *Cardiol Clin* 2000;18:597–617
4. Zannad F, Dousset B, Alla F: Treatment of congestive heart failure, interfering the aldosterone-cardiac extracellular matrix relationship. *Hypertension* 2001;38:1227–1232
5. Brilla C, Weber K: Reactive and reparative myocardial fibrosis in arterial hypertension in rats. *Cardiovasc Res* 1992;26:671–677
6. Young M, Funder J: Determinants of cardiac fibrosis in experimental hypermineralocorticoid states. *Am J Physiol* 1995;269:E657–662
7. Delcayre C, Silvestre JS: Review: Aldosterone and the heart: Towards a physiological function? *Cardiovasc Res* 1999;43:7–12
8. Brilla C, Matsubara LS, Weber KT: Antifibrotic effects of spironolactone in preventing myocardial fibrosis in systemic arterial hypertension. *Am J Cardiol* 1993;71:12A–16A
9. Lijnen P, Petrov V: Antagonism of the renin angiotensin aldosterone system and collagen metabolism in cardiac fibroblasts. *Method Find Exp Clin Pharmacol* 1999;21:215–227
10. Silvestre J, Heymes C, Oubenaissa A, Robert V, Aupetit-Faisant B, Carayon A, Swynghedauw B, Delcayre C: Activation of cardiac aldosterone production in rat myocardial infarction: Effect of angiotensin II receptor blockade and role in cardiac fibrosis. *Circulation* 1999;99:2694–2701
11. Lacolley P, Safer ME, Lucet B, Ledudal K, Labat C, Benetos A: Prevention of aortic and cardiac fibrosis by spironolactone on old normotensive rats. *J Am Coll Cardiol* 2001;37:662–667
12. Sato A, Hayashi M, Saruta T: Relative long-term effects of spironolactone in conjunction with angiotensin-converting enzyme inhibitors on left ventricular mass and diastolic function in patients with essential hypertension. *Hypertens Re*s 2002;25:837–842
13. Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH: Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. *Circulation* 2004;110:558–565
14. Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ, Labarthe D: Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995;25:305–313
15. Tsutamoto T, Wada A, Maeka K, Mabuchi N, Hayashi M, Tsutsui T, Ohnishi M, Sawaki M, Fujii M, Matsumoto T, Matsui T, Kinoshita M: Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *J Am Coll Cardiol* 2001;37:1228–1233
16. Querejeta R, Varo N, Lopez B, Larman M, Artinano E, Etayo JC, Martinez Ubago JI, Gutierrez-Stampa M, Emparanza JI, Gil MJ, Monreal I, Mindan JP, Diez J: Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. *Circulation* 2000;101:1729–1735
17. Querejeta R, Lopez B, Gonzalez A, Sanchez E, Larman M, Martinez Ubago JL, Diez J: Increased collagen type I synthesis in patients with heart failure of hypertensive origin: Relation to myocardial fibrosis. *Circulation* 2004; 110:1263–1268
18. Zannad F, Alla F, Dousset B, Perez A, Pitt B: Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: Insights from the Randomized Aldactone Evaluation Study (RALES). *Circulation* 2000;102: 2700–2706