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Original Article

Retrospective study on the short-term efficacy of different doses of Spironolactone in patients with heart failure of ischemic cardiomyopath and the influence of ventricular remodeling markers

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Abstract: Objective: To evaluate the impact of varying dosages of Spironolactone on the short-term effectiveness and ventricular remodeling indicators in patients with Heart Failure of Ischemic Cardiomyopathy (HFIC). Methods: A cohort of 141 HFIC patients, admitted to our hospital between October 2018 and February 2023, were enrolled for this study. Alongside the standard treatment for Chronic Congestive Heart Failure (CHF), these patients were randomly assigned to either a low-dose (20 mg/d, N=70) or a high-dose (60 mg/d, N=71) Spironolactone group. After four weeks, various parameters were assessed and compared within each group before and after the treatment. These parameters included echocardiographic indices (LVEF, LVESD, LVEDD, LVESV, and LVEDV), New York Heart Association (NYHA) cardiac function classification, ventricular remodeling markers (hs-CRP, TNF-α, NT-pro BNP, Gal-3, MMP-9, and TIMP-4), and the Six Minute Walk Distance (6MWD). Results: Both low-dose and high-dose Spironolactone significantly improved LVEF and 6MWD in HFIC patients ($P<0.05$), as well as markedly reduced LVESD, LVEDD, LVESV, LVEDV, and NYHA cardiac function grades ($P<0.05$). The high-dose group exhibited the most pronounced improvements ($P<0.05$). High-dose Spironolactone was more effective in improving the clinical and total effective rate compared to the low-dose, significantly reducing treatment inefficacy ($P<0.05$). Both dosages significantly increased serum potassium levels within normal ranges. They also improved the expression of ventricular remodeling markers (hs-CRP, TNF-α, NT-pro BNP, Gal-3, MMP-9, and TIMP-4) in HFIC patients, with the high-dose group showing the most significant results ($P<0.05$). Conclusion: High-dose Spironolactone (60 mg/d) demonstrates superior efficacy over the low-dose (20 mg/d) in rapidly diminishing ventricular remodeling damage and enhancing cardiac function and clinical symptoms in HFIC patients over a short duration.

Keywords: Heart failure of ischemic cardiomyopath, spironolactone, chronic congestive heart failure, renin angiotensin aldosterone system, ventricular remodeling, cardiac function

Introduction

Chronic Congestive Heart Failure (CHF), often resulting from ischemic cardiomyopathy, is attributed to various factors including myocardial hibernation, myocardial infarction, and sporadic fibrosis. This condition is characterized by a high incidence rate and mortality, posing a significant threat to patient survival [1-3]. Consequently, it is imperative for clinicians to focus on the intervention and treatment of HFIC. Selecting an appropriate and efficacious treatment strategy is crucial for enhancing patient prognosis and extending survival [4, 5]. Contemporary research indicates that the pathophysiology of CHF may involve several mechanisms: reduced effective arterial blood volume, increased peripheral vascular resistance reflex, activation of the sympathetic nervous system, and stimulation of the Renin Angiotensin Aldosterone System (RAAS). These processes contribute to water and sodium retention, elevated plasma blood volume, and accelerated vascular and left ventricular remodeling, thereby exacerbating heart failure [5, 6]. Studies have shown that inhibiting RAAS activation is fundamental in CHF treatment, significantly enhancing therapeutic outcomes and preventing ventricular remodeling [6, 7].

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Currently, the clinical application of Angiotensin-Converting Enzyme Inhibitors (ACEI) in RAAS effectively reduces circulating aldosterone levels, but instances of aldosterone may escape are reported, with some studies suggesting this occurs in up to 38% of cases [8, 9]. Evidence indicates that integrating Spironolactone into conventional CHF therapy can substantially mitigate the aldosterone escape phenomenon [10, 11]. Additionally, Spironolactone has been found to enhance cardiac function in CHF patients, decelerate heart failure progression, inhibit myocardial fibrosis, and ameliorate ventricular remodeling [12, 13].

Contemporary research associates ventricular remodeling with several biomarkers, including NT proBNP, hs-CRP, TNF-α, Matrix Metalloproteinases (MMPs), Tissue Inhibitors of Metalloproteinases (TIMPs), and Gal-3 [14, 15]. However, the specific impacts of different Spironolactone dosages on the short-term clinical management of HFIC and ventricular remodeling indices remain under-explored. This paper, therefore, examines the short-term therapeutic effects of varied Spironolactone doses on HFIC and ventricular remodeling indicators (NT proBNP, hs-CRP, TNF-α, IL-6, MMPs, TIMPs, and Gal-3). The objective is to ascertain the optimal Spironolactone dosage for the short-term improvement of HFIC.

Materials and methods

Inclusion and exclusion criteria

A total of 141 patients diagnosed with HFIC at the Second Affiliated Hospital of the Army Medical University, from October 2018 to February 2023, were selected for this study. The cohort comprised 79 males and 62 females, with an average age of 66.76±7.53 years. Inclusion criteria included: ① Diagnosis of HFIC according to the European Heart Association's criteria, confirmed by ultrasound evidence of significant heart enlargement and recurrent heart failure [16]; ② Heart function classified as III-IV by the New York Heart Association (NYHA). Exclusion criteria encompassed: ① Patients with non-ischemic cardiomyopathy-induced heart failure; ② Recent history (within three months) of acute coronary syndrome; ③ Severe liver or kidney dysfunction; ④ Serum potassium levels ≥5.0 mmol/L; ⑤ Severe diabetes, hyperthyroidism, atrioventricular block, presence of a permanent pacemaker, or malignant tumors.

The 141 HFIC patients were randomly assigned into two groups: a low-dose Spironolactone group (20 mg/d, N=70) and a high-dose Spironolactone group (60 mg/d, N=71). In addition to standard treatments including β receptor blockers, aspirin, ACEI, and furosemide, the low-dose group received 20 mg of Spironolactone daily, while the high-dose group received 60 mg daily. The intervention's effects were observed four weeks later. This study was conducted with the approval of the Ethics Committee of the Second Affiliated Hospital of the Army Medical University. Informed consent was obtained from all patients and their families.

Observation indicators

Prior to and following treatment, patients in both groups underwent color Doppler echocardiography using a Madison SonoAce X8 model. This examination included measurements of the left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and left ventricular ejection fraction (LVEF). Additionally, fasting venous blood samples were collected from patients in both groups in the morning, before and after treatment, to analyze changes in serum potassium, transaminase, creatinine, and urea levels. The levels of high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor α (TNF-α), N-terminal brain natriuretic peptide precursor (NT-pro BNP), matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase 4 (TIMP-4), and Galectin-3 (Gal-3) in patients from both groups were measured using an ELISA kit (Elabscience, Wuhan, China), both before and after the treatment period. Furthermore, the Six Minute Walk Distance (6MWD) and New York Heart Association (NYHA) cardiac function classification were recorded and analyzed for patients in both groups before and after treatment.

Evaluation criterion

In this study, cardiac function is assessed using the NYHA cardiac function grading, categorizing patients into Classes I to IV based on the

Table 1. Comparison of general clinical data between two groups of patients

Parameter		Low-dose group (n=70)	High-dose group (n=71)	*P* value
Gender	Male	38 (54.29%)	41 (58.57%)	
	Female	32 (45.71%)	30 (42.25%)	0.532
Age		65.98±7.35	66.24±6.92	0.834
NYHA Cardiac Function Classification	III	31 (44.28%)	33 (47.14%)	
	IV	39 (55.71%)	38 (54.28%)	0.319

NYHA: New York Heart Association.

Table 2. The changes of serum potassium, transaminase, creatinine and urea in the two groups before and after treatment

Parameter		Low-dose group (n=70)	High-dose group (n=71)
ALT, (U/L)	Before treatment	31.82±8.72	32.91±9.37
	After treatment	32.01±7.58	33.81±8.78
AST, (U/L)	Before treatment	30.04±6.55	29.76±6.75
	After treatment	29.64±7.15	31.04±6.05
Serum creatinine (μmol/L)	Before treatment	82.04±13.76	84.24±12.96
	After treatment	79.83±13.05	81.27±13.78
Serum urea (mmol/L)	Before treatment	4.97±1.51	5.14±1.12
	After treatment	4.79±1.76	4.94±1.38
Serum potassium (mmol/l)	Before treatment	3.01±0.69	3.13±0.78
	After treatment	3.41±1.07*	3.87±1.26*,Δ

*P<0.05: Comparison between groups after treatment and before treatment.
ΔP<0.05: Comparison between high-dose group and low-dose group.

presence and severity of heart failure symptoms, from no symptoms in daily activities (Class I) to symptoms at rest (Class IV) [17]. The criteria for evaluating treatment efficacy are defined as: significant improvement (complete relief of heart failure symptoms, notable improvement in clinical signs, and an increase of 2 or more levels in NYHA grading), effectiveness (partial relief of heart failure symptoms but still present during daily activities, and a one-level increase in NYHA grading), and ineffectiveness (no significant improvement in clinical signs or cardiac function, or a decrease in cardiac function). The total effective rate of clinical treatment is calculated by the formula: (number of patients with significant improvement + number of patients with effectiveness)/ total number of cases × 100%. The 6MWD test further classifies patients' cardiopulmonary function into four levels: Level I (<300 meters), Level II (300-375 meters), Level III (>375-450 meters), and Level IV (>450 meters), with lower levels indicating poorer cardiopulmonary function and Level III or above suggesting that the patient's cardiac function is close to or meets normal standards [18, 19].

Statistics analysis

Data processing in this study was conducted using the SPSS 20.0 statistical software package. To ascertain the normal distribution of continuous variables, the K-S (Kolmogorov-Smirnov) single-sample test was employed prior to conducting further comparisons. Measurement data were presented as mean ± standard deviation. The T-test was utilized for comparing measurement data between groups. Count data were expressed in numbers or percentages, and intergroup comparisons for these were made using the χ^2 (Chi-square) test. The rank sum test was applied for analyzing ranked data. A *p*-value of less than 0.05 was considered indicative of a statistically significant difference.

Result

Comparison of general clinical data between two groups of patients

Table 1 illustrates that there were no statistically significant differences (P>0.05) between the two groups in terms of age, gender, and NYHA cardiac function grading. This outcome indicates that the clinical baseline data of the patients in both groups are comparable.

The changes of serum potassium, transaminase, creatinine and urea in the two groups before and after treatment

Table 2 reveals that there were no significant differences in serum transaminase, creatinine, and urea levels between the two groups before and after treatment (P>0.05). However, post-

Table 3. Changes of echocardiography results before and after treatment in two groups

Parameter		LVESD (mm)	LVEDD (mm)	LVESV (ml)	LVEDV (ml)	LVEF (%)
Low-dose group (n=70)	Before treatment	55.08±6.15	62.92±7.68	61.85±8.12	122.56±15.05	31.29±6.04
	After treatment	49.28±6.31*	58.42±7.89*	53.01±7.65*	108.65±9.54*	48.12±7.56*
High-dose group (n=71)	Before treatment	56.18±6.75	63.38±7.24	62.05±7.96	125.04±13.93	31.05±6.28
	After treatment	45.58±6.43*,Δ	54.92±7.09*,Δ	48.61±7.65*,Δ	90.25±9.02*,Δ	52.62±7.56*,Δ

LVESD: left ventricular end systolic diameter; LVEDD: left ventricular end-diastolic diameter; LVESV: left ventricular end-systolic volume; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction. *P<0.05: Comparison between groups after treatment and before treatment. ΔP<0.05: Comparison between high-dose group and low-dose group.

Table 4. Changes in NYHA cardiac function grading and six-minute walk distance before and after treatment in two groups of patients

Parameter		NYHA Cardiac Function Classification	6-minute walking distance
Low-dose group (n=70)	Before treatment	3.71±0.34	311.02±22.25
	After treatment	2.45±0.57*	371.2±24.92*
High-dose group (n=71)	Before treatment	3.68±0.37	320.7±22.85
	After treatment	1.98±0.67*,Δ	419.3±25.64*,Δ

*P<0.05: Comparison between groups after treatment and before treatment.
ΔP<0.05: Comparison between high-dose group and low-dose group.

treatment comparisons showed a significant increase in serum potassium levels in both the low-dose (from 3.01±0.69 to 3.41±1.07, P< 0.05) and high-dose (from 3.13±0.78 to 3.87±1.26, P<0.05) groups. Furthermore, the serum potassium levels in the high-dose group were higher compared to the low-dose group (3.87±1.26 vs 3.41±1.07, P<0.05). It is notable that despite these increases, the serum potassium levels in both groups remained within the normal range.

Changes in echocardiographic results before and after treatment in two groups of patients

As shown in **Table 3**, there was no significant difference in LVESD, LVESD, LVESV, LVEDV and LVEF between the two groups of patients before treatment (P>0.05). Post-treatment, both groups showed a significant increase in LVEF (P<0.05) and notable reductions in LVESD, LVEDD, LVESV, and LVEDV (P<0.05) compared to pre-treatment values. Compared with the low-dose group, the high-dose group showed a significant increase in LVEF (52.62±7.56 vs 48.12±7.56, P<0.05), while LVESD (45.58±6.43 vs 49.28±6.31, P<0.05), LVEDD (54.92±7.09 vs 58.42±7.89, P<0.05), LVESV (48.61±7.65 vs 53.01±7.65, P<0.05) and LVEDV (90.25±9.02 vs 108.65±9.54, P<0.05) were significantly reduced.

Changes in NYHA cardiac function grading and six-minute walk distance before and after treatment in two groups of patients

Table 4 shows that before treatment, there were no significant differences in the NYHA cardiac function grading or the 6MWD between the two groups of patients (P>0.05). However, post-treatment comparisons revealed significant improvements in both groups: the 6MWD substantially increased (P<0.05), and the NYHA cardiac function grading notably decreased (P<0.05). When comparing the two groups, the high-dose group demonstrated a more significant increase in 6MWD (419.3±25.64 vs 371.2±24.92, P<0.05) and a greater reduction in NYHA cardiac function grading (1.98±0.67 vs 2.45±0.57, P<0.05) compared to the low-dose group.

Changes in expression of ventricular remodeling indicators before and after treatment in two groups of patients

As shown in **Table 5**, there was no statistically significant difference in hs-CRP, TNF-α, NT-pro BNP, Gal-3, TIMP-4 and MMP-9 between the two groups of patients before treatment (P> 0.05). After treatment, both groups exhibited significant decreases in hs-CRP, TNF-α, NT-pro BNP, Gal-3, and MMP-9 (P<0.05), while TIMP-4 levels significantly increased (P<0.05). When comparing the two groups post-treatment, there were no statistically significant differences in hs-CRP (2.98±0.64 vs 3.01±0.56, P>0.05) and TNF-α (9.83±0.89 vs 10.43±0.78, P>0.05) in the high-dose group compared to the low-dose group. However, the levels of Gal-3 (2.96±0.49 vs 4.72±0.58, P<0.05), MMP-9 (164.35±46.39

Table 5. Changes in expression of ventricular remodeling indicators before and after treatment in two groups of patients

Parameter		hs-CRP (mmol/L)	TNF-α (pg/ml)	NT-pro BNP (pg/ml)	Gal-3 (ng/ml)	TIMP-4 (μg/L)	MMP-9 (μg/L)
Low-dose group (n=70)	Before treatment	9.14±0.76	43.10±4.73	611.46±135.24	11.50±1.49	62.77±7.14	457.08±70.67
	After treatment	3.01±0.56*	10.43±0.78*	189.39±44.78*	4.72±0.58*	112.46±11.95*	289.55±48.09*
High-dose group (n=71)	Before treatment	9.26±0.78	42.70±5.17	621.06±126.52	11.67±1.38	62.07±8.34	450.12±73.12
	After treatment	2.98±0.64*	9.83±0.89*	104.59±53.08*,Δ	2.96±0.49*,Δ	159.86±12.55*,Δ	164.35±46.39*,Δ

hs-CRP: high sensitive C reactive protein; TNF-α: tumor necrosis factor α; NT-pro BNP: N-terminal brain natriuretic peptide precursor; MMP-9: matrix metalloproteinase-9; TIMP-4: matrix metalloproteinase inhibitor 4; Gal-3: Galectin-3. *P<0.05: Comparison between groups after treatment and before treatment. ΔP<0.05: Comparison between high-dose group and low-dose group.

Table 6. Comparison of clinical efficacy between two groups of patients

Parameter	Clinically significantly effective rate	Clinically effective rate	Treatment ineffective rate	Total effective rate
Low-dose group (n=70)	24 (34.29%)	30 (42.85%)	16 (22.85%)	58 (78.57%)
High-dose group (n=71)	33 (46.48%)Δ	32 (45.07%)	8 (11.27%)Δ	65 (91.55%)Δ

ΔP<0.05: Comparison between high-dose group and low-dose group.

vs 289.55±48.09, P<0.05), and NT-pro BNP (104.59±53.08 vs 189.39±44.78, P<0.05) were significantly lower, while TIMP-4 (159.86±12.55 vs 112.46±11.95, P<0.05) was significantly higher in the high-dose group compared to the low-dose group.

Comparison of clinical efficacy between two groups of patients

Compared with the low-dose group **Table 6**, the high-dose group showed a significant increase in clinically significantly effective rate (46.48% vs 34.29%, P<0.05) and total effective rate (91.55% vs 78.57%, P<0.05), while the treatment ineffective rate was significantly reduced (11.27% vs 22.85%, P<0.05).

Discussion

The prolonged overactivation of the Renin Angiotensin Aldosterone System (RAAS) is implicated as a significant factor in the onset and progression of HFIC, and it plays a critical role in the exacerbation of CHF [20]. Targeting the inhibition of RAAS activation is central to heart failure management and can enhance the treatment efficacy of CHF [5-7]. Spironolactone, due to its structural similarity to aldosterone, can competitively bind to aldosterone receptors in the distal convoluted tubules and collecting ducts of the kidney. This antagonizes the sodium-water retention effects of aldosterone and inhibits the transformation of angiotensin II type 1 receptor into angiotensin II type 2 receptor. Such mechanisms effectively prevent aldosterone escape, significantly ameliorating clinical symptoms and ventricular remodeling in CHF [21, 22]. The RALES trial provided evidence that long-term use of Spironolactone in CHF patients can improve vascular endothelial function, prevent aldosterone escape, decrease myocardial fibrosis, and reduce all-cause mortality in CHF patients by 30% and cardiogenic mortality by 31% [23]. However, determining the optimal dosage of Spironolactone for treating HFIC remains an area for further investigation and discussion.

Currently, many scholars recommend the long-term use of low-dose Spironolactone to mitigate ventricular remodeling and enhance the quality of life in patients with CHF [24]. However, in the early stages of HFIC, rapidly reducing the circulatory load and the expression of ventricular remodeling damage molecules, blocking the activation of the RAAS, and preventing and treating ventricular remodeling to improve clinical symptoms are of substantial clinical importance. Some scholars, acknowledging this, have employed high doses of Spironolactone in CHF treatment, finding that such doses can rapidly improve clinical symptoms and cardiac function [25, 26]. However, the effects of different Spironolactone dosages on short-term clinical treatment of HFIC and ventricular remodeling indices have not been extensively reported.

In this study, we investigated the impact of high-dose Spironolactone (60 mg/d) on cardiac function, clinical symptoms, and the expression of damage molecules related to ventricular remodeling in HFIC. We observed that both low-dose and high-dose Spironolactone significantly enhanced LVEF and 6MWT distance, and markedly reduced LVESD, LVEDD, LVESV, LVEDV, and NYHA cardiac function grades, with the high-dose group showing the most significant improvement. Regarding clinical efficacy, both low and high doses of Spironolactone can improve the clinically significant effective rate and total effective rate in HFIC patients. Notably, compared to low-dose Spironolactone, high-dose Spironolactone significantly enhanced the clinical effective rate and total effective rate and reduced treatment inefficiency in HFIC patients. This result might be attributed to the high-dose Spironolactone's rapid antagonism of the aldosterone system, preventing aldosterone escape, reducing water and sodium retention, lowering cardiac preload, and thus improving cardiac function in HFIC patients.

Furthermore, this study found no significant impact of either high or low doses of Spironolactone on serum transaminase, creatinine, and urea levels. Post-treatment, serum potassium levels increased in HFIC patients treated with both dosages, but no hyperkalemia was observed in any group, with serum potassium values remaining within normal ranges. These findings align with literature reports, suggesting that high doses of Spironolactone can rapidly ameliorate clinical symptoms and cardiac function in HFIC patients without increasing the risk of hyperkalemia [27, 28].

Current research underscores that ventricular remodeling is a crucial factor in the development and progression of HFIC, and it's closely linked to the worsening and poor prognosis of HFIC patients [14, 15, 30, 31]. Research has also found that hs-CRP, TNF-α, MMP-9, TIMP-4, Gal-3 and NT-pro BNP are closely related to ventricular remodeling [14, 15, 30, 31]. Elevated levels of hs-CRP and TNF-α can promote myocardial inflammatory cell infiltration, accelerate myocardial cell apoptosis and necrosis, leading to myocardial fibrosis and ventricular remodeling [14, 15]. Serum MMP-9 concentration is positively correlated with adverse ventricular remodeling, while TIMP-4 levels are inversely related [30, 31]. High MMP-9 concentrations are indicative of poor ventricular remodeling [30, 31]. Gal-3 is predictive of cardiac function changes and plays a role in multi-organ fibrosis formation, being a marker of heart failure and myocardial fibrosis [32]. Elevated Gal-3 levels are associated with poor ventricular remodeling and prognosis [32]. NT-pro BNP, primarily derived from the ventricles, has its expression level directly proportional to the extent of cardiac dysfunction, holding significant clinical value in cardiac function assessment and prognosis prediction [33]. Additionally, high NT-pro BNP expression is implicated in ventricular remodeling [33].

In this study, we observed that post-treatment, HFIC patients exhibited significant reductions in hs-CRP, TNF-α, NT-pro BNP, Gal-3, and MMP-9, while TIMP-4 significantly increased. When comparing the two dosages, there was no significant difference in hs-CRP and TNF-α levels between the high-dose and low-dose groups. However, Gal-3, MMP-9, and NT-pro BNP levels were significantly lower, and TIMP-4 significantly higher, in the high-dose group. These results suggest that a 60 mg/d dosage of Spironolactone can rapidly reduce the expression of ventricular remodeling molecules and is more effective than the lower dosage in preventing ventricular remodeling and myocardial fibrosis.

In summary, our research suggests that high doses of Spironolactone may effectively antagonize the Aldosterone system, prevent Aldosterone escape, lessen water and sodium retention, reduce cardiac preload and ventricular wall tension, and decrease the expression of ventricular remodeling molecules, thereby positively impacting myocardial fibrosis and ventricular remodeling. However, this study has several limitations, including a small sample size that could introduce bias, inherent limitations in the study design which may affect the results, a short follow-up and observation period that requires further validation in longer-term studies with larger cohorts, and the absence of dynamic detection of ventricular remodeling marker molecules.

Conclusion

High-dose Spironolactone (60 mg/d) has demonstrated superiority over low-dose Spirono-

lactone (20 mg/d) in rapidly diminishing the expression of ventricular remodeling markers and enhancing cardiac function and clinical symptoms in patients with HFIC over a short timeframe. Nonetheless, the question of whether the long-term use of 60 mg Spironolactone offers better outcomes than 20 mg Spironolactone requires further in-depth investigation and exploration to establish a more definitive conclusion.

Disclosure of conflict of interest

None.

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