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Original Article

Metoprolol-spironolactone combination for coronary heart disease with concurrent heart failure: impact on cardiac function

Shujun Zhao*, Jiwei Zhang*, Yansha Zhao

Department of Cardiovascular Medicine, Affiliated Hospital of Hebei University, Baoding 071000, Hebei, China.
**Equal contributors and co-first authors.*

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Abstract: Objective: This study intended to clarify the role of metoprolol-spironolactone combination in treating coronary heart disease (CHD) with concurrent heart failure (HF), focusing on its impact on cardiac function. Methods: A total of 100 CHD + HF patients were selected, including 50 cases in the control group treated with spironolactone and 50 cases in the research group given metoprolol + spironolactone. Cardiac function (left ventricular end-systolic diameter [LVESd], left ventricular end-diastolic diameter [LVEDd], left ventricular ejection fraction [LVEF]), cardiac function classification, serum brain natriuretic peptide (BNP), oxidative stress (superoxide dismutase [SOD], malondialdehyde [MDA]), inflammation, hemodynamics (cardiac index/output), effectiveness, and safety were analyzed. Results: The combination therapy induced a more evident reduction in LVESd, LVEDd, BNP, MDA, and two inflammatory cytokines than spironolactone alone, as well as a greater rise in LVEF, SOD, cardiac index, and cardiac output. The research group also showed superior improvements in cardiac function classification and clinical efficacy, as well as a lower overall adverse effect rate. Conclusion: Metoprolol-spironolactone combination is remarkably effective in treating CHD + HF and significantly improve patients' cardiac function, which merits clinical popularization.

Keywords: Metoprolol, spironolactone, coronary heart disease, heart failure, cardiac function

Introduction

Coronary heart disease (CHD) is a chronic immune inflammatory, fibroproliferative disease, driven by lipid abnormalities, which will cause arterial stenosis and blockage, further causing myocardial hypoxia and ischemia [1, 2]. If the disease is not treated timely and effectively, it may be complicated with heart failure (HF), which further worsens the condition and seriously affects the patient's cardiac function [3]. As a progressive clinical syndrome, HF mainly manifests as fatigue, dyspnea, and ankle swelling, and may also be accompanied by lung moist rales, peripheral edema, and elevated jugular venous pressure. HF only occurs when the symptoms are obvious [4, 5]. The etiology of HF is related to structural and/or functional cardiac abnormalities, and its risk factors include coronary heart disease, hypertension, diabetes, obesity, metabolic disease, alcohol abuse, etc. [6]. CHD + HF patients often have high 3-year all-cause mortality, which is extremely unfavorable for their prognoses [7]. At present, there is still room for optimization in the drug treatment of CHD + HF. This study will further optimize the treatment of such patients from the perspective of drug treatment.

Spironolactone is a synthetic aldosterone receptor antagonist. It can be used to treat androgenic alopecia by reducing total testosterone levels and blocking androgen receptors in target tissues. It can also be used in female patients to treat testosterone-related acne and hirsutism [8, 9]. Studies have shown that spironolactone has multiple effects such as inhibiting inflammation, fibrosis, and thrombosis, as well as improving vascular function. These effects, to some extent, contribute to the cardiovascular protective effect and are beneficial for controlling the condition of CHD complicated with HF [10]. Spironolactone, compared to placebo, increases the risk of renal function dete-

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rioration in patients with preserved ejection fraction heart failure, but it can reduce the cardiovascular death risk [11]. Metoprolol, as a β-adrenergic receptor antagonist, can be used in treating various cardiovascular diseases, thyroid crises, and localized choroidal angiomas [12, 13]. In a CHD rat model, metoprolol is beneficial in alleviating myocardial injury, inhibiting inflammation, oxidative stress, and myocardial apoptosis, and alleviating myocardial ischemia, aiding in preventing CHD progression [14]. Also, Dave et al. [15] reported the application of metoprolol in HF patients, noting its safety without significantly elevating the risk of clinically relevant hyperglycemia. An animal experiment in hamsters with dilated cardiomyopathy has reported the ability of metoprolol plus spironolactone to synergistically enhance cardiac remodeling [16]. In the report of Dabrowski et al. [17], spironolactone combined with β-adrenoceptor antagonists proves beneficial in reducing atrial fibrillation attacks and improving left ventricular function in refractory paroxysmal atrial fibrillation patients. Given the few investigations into the clinical study of metoprolol + spironolactone in treating CHD + HF comorbidity, our research is innovative to some extent.

This study focuses on the impact of the metoprolol-spironolactone combination in CHD + HF treatment, particularly on cardiac function. At present, there is little research on this aspect, and this study adds supplementary value to this topic.

Information and methodology

Participants

This retrospective study has been approved by the Ethics Committee of the Affiliated Hospital of Hebei University. We enrolled 100 CHD-HF patients admitted from February 2022 to May 2024. The control group (n=50) received spironolactone, while the research group (n=50) received additional metoprolol therapy. Clinical comparability was demonstrated by the balanced baseline characteristics across groups (P>0.05).

Inclusion and exclusion criteria

Included patients had CHD and HF confirmed by imaging, laboratory indexes and clinical symptoms, with persistent symptoms (e.g., fatigue, dyspnea > 6 months). They were all classified as II-IV per the New York Heart Association (NYHA) criteria, were hemodynamically stable, and had accessible complete medical records.

Exclusions included pre-enrollment treatment with steroid hormones, non-steroidal anti-inflammatory drugs, or other similar medications, infections/autoimmune conditions, significant organ dysfunction (e.g., cardiac, pulmonary, or renal insufficiency), malignancies, allergies or contraindications to the study medications, psychiatric comorbidities, or mental disorders.

Treatment methods

All patients received basic care such as diuretics and vasodilators after admission. Specifically, the diuretic was administered orally as furosemide. The initial dose was 20-40 mg per day, adjusted based on the daily urine output and edema condition, to maintain a euvolemic state. Isosorbide mononitrate was the vasodilator administered, which was taken orally, 20 mg/time, twice/day. The control group was given oral spironolactone (20 mg per dose, twice daily) for three months. The research group received additional metoprolol (12.5 mg/dose, twice daily) for the same period.

Detection indicators

(1) Cardiac function indicators: Pre- and post-intervention (3 months) measurements of left ventricular (LV) function (LV end-systolic diameter [LVESd], LV end-diastolic diameter [LVEDd], and LV ejection fraction [LVEF]) were obtained utilizing a full-digital color Doppler ultrasound apparatus.

(2) Cardiac function classification: The classification was determined 3 months post-intervention following the standards established by the NYHA: Grade I: Patients were able to engage in unrestricted physical activity; no symptoms such as fatigue, dyspnea, palpitations, shortness of breath, or angina occur during routine physical exertion. Grade II: The patient's physical activity was slightly restricted; symptoms such as fatigue, shortness of breath, palpitations, or angina pectoris occurred during regular physical exertion but subsided during rest. Grade III: The patient had significant limitations

Table 1. Comparison of general information

Indicators	Control group (n=50)	Research group (n=50)	χ^2/t	P
Age (years)	65.28±7.30	62.74±6.53	1.834	0.070
CHD course (years)	8.38±3.44	8.90±3.44	0.756	0.452
HF course (months)	24.70±10.93	27.94±10.56	1.507	0.135
Cardiac function classification			1.090	0.580
II	18 (36.00)	16 (32.00)		
III	25 (50.00)	23 (46.00)		
IV	7 (14.00)	11 (22.00)		
Family medical history			1.000	0.317
Yes	12 (24.00)	8 (16.00)		
No	38 (76.00)	42 (84.00)		

Note: CHD, coronary heart disease; HF, heart failure.

in physical activity; even minor physical exertion can trigger symptoms such as shortness of breath or palpitations, although such symptoms do not occur during rest. Grade IV: The patient experiences shortness of breath, palpitations, angina pectoris, and cardiac insufficiency during rest, and is unable to tolerate any form of physical activity.

(3) Serum brain natriuretic peptide (BNP): Before therapy initiation and three months post-treatment, 5 ml of fasting venous blood was collected from patients in the morning, and the plasma was taken after centrifugation. The BNP level was measured by electrochemiluminescence immunoassay with a full-automatic biochemical analyzer.

(4) Oxidative stress: Before and 3 months after the intervention, 5 ml fasting peripheral venous blood was collected early in the morning and centrifuged routinely, with the supernatant used for examination. Superoxide dismutase (SOD) and malondialdehyde (MDA) were measured by enzyme-linked immunosorbent assay (ELISA) and the thiobarbituric acid method, respectively.

(5) Inflammatory factors: Pre- and post-interventional (at the 3-month mark) interleukin-6 (IL-6) and C-reactive protein (CRP) were measured using ELISA protocol.

(6) Hemodynamics: A clinical hemodynamic analyzer was employed to examine cardiac index and cardiac output, also before and 3 months following the intervention.

(7) Clinical efficacy: The assessment was conducted 3 months post-therapy. Criteria: Markedly effective: the NYHA cardiac function grade decreased by ≥2 grades, clinical symptoms resolved, and physical signs normalized. Effective: the NYHA cardiac function grade reduced by 1 grade, and symptoms and signs were significantly improved. Ineffective: the patient's condition did not meet the above standards or even worsened. The overall effective rate = markedly effective rate + effective rate.

(8) Safety assessment: The instances of palpitations, nausea, fatigue, and dizziness during treatment, as well as the total incidence, were counted.

Statistical methods

Data are presented as mean ± SD (for continuous data) or n (%) (for categorical data). Group comparisons employed independent or paired t-tests for continuous variables and chi-square tests for categorical data. SPSS 20.0 was the statistical tool used, and the significance level adopted was $P<0.05$.

Results

General data comparison

Age, course of CHD and HF, cardiac function grade, family history, and other general data did not differ statistically between groups ($P>0.05$; **Table 1**).

Comparative assessment of cardiac function

The groups were similar in pre-interventional LVESd, LVEDd, and LVEF ($P>0.05$). Post-intervention, decreased LVESd and LVEDd and ele-

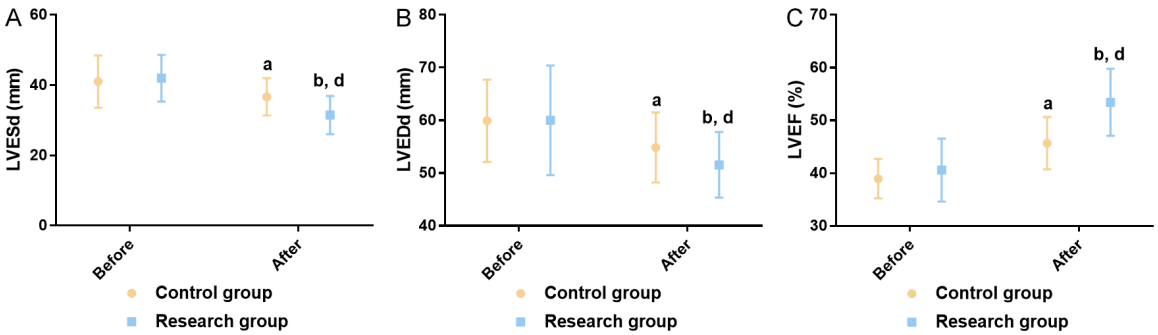

Figure 1. Cardiac function indicators in the control and research groups. A. LVESd in control vs. research group. B. LVEDd across groups. C. LVEF in two cohorts. Note: LVESd, left ventricular end-systolic diameter; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction. [a]P<0.05, [b]P<0.01 vs. pre-intervention; [d]P<0.05 vs. control group.

Table 2. Comparison of cardiac functional classification between groups

Indicators	Control group (n=50)	Research group (n=50)	χ^2	P
Grade I	3 (6.00)	11 (22.00)	5.316	0.021
Grade II	18 (36.00)	30 (60.00)	5.769	0.016
Grade III	20 (40.00)	7 (14.00)	8.574	0.003
Grade IV	9 (18.00)	2 (4.00)	6.519	0.011

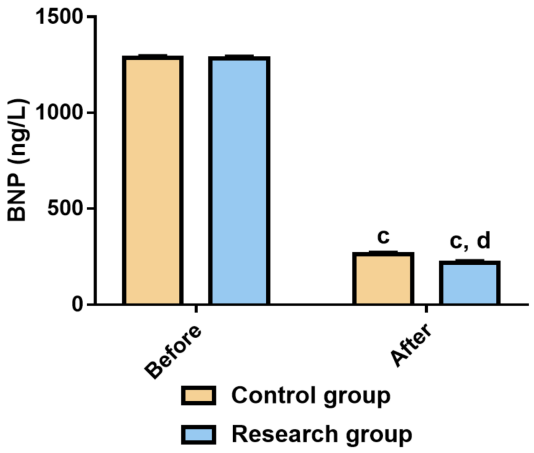

Figure 2. Intergroup comparison of BNP. Note: BNP, brain natriuretic peptide. [c]P<0.001 vs. pre-intervention; [d]P<0.05 vs. control group.

vated LVEF were noted in both cohorts (P<0.05), with a greater change amplitude in the research group versus controls (P<0.05; **Figure 1**).

Cardiac function classification in the research group

According to the inter-group analysis, the research group had more patients classified as Grade I/II and considerably fewer Grade III/IV cases (P<0.05) compared to controls (**Table 2**).

BNP comparison

Baseline BNP showed no notable between-group difference (P>0.05). BNP decreased in both groups post-intervention (P<0.05), especially in the research group (P<0.05; **Figure 2**).

Assessment of oxidative stress parameters between groups

The groups differed little in pre-interventional SOD and MDA (P>0.05). A post-treatment rise in SOD and decline in MDA were noted across groups (P<0.05), with the research group exhibiting elevated SOD and reduced MDA than controls (P<0.05; **Figure 3**).

Inflammatory cytokine profiles in both cohorts

IL-6 and CRP levels were similar between the cohorts at baseline (P>0.05). Both groups exhibited reductions in these markers post-intervention (P<0.05), with the research group achieving lower levels (P<0.05; **Figure 4**).

Comparison of hemodynamics

Cardiac index and output were comparable between groups pre-treatment (P>0.05). Both measures exhibited a rise in both cohorts after intervention (P<0.05), with greater increases

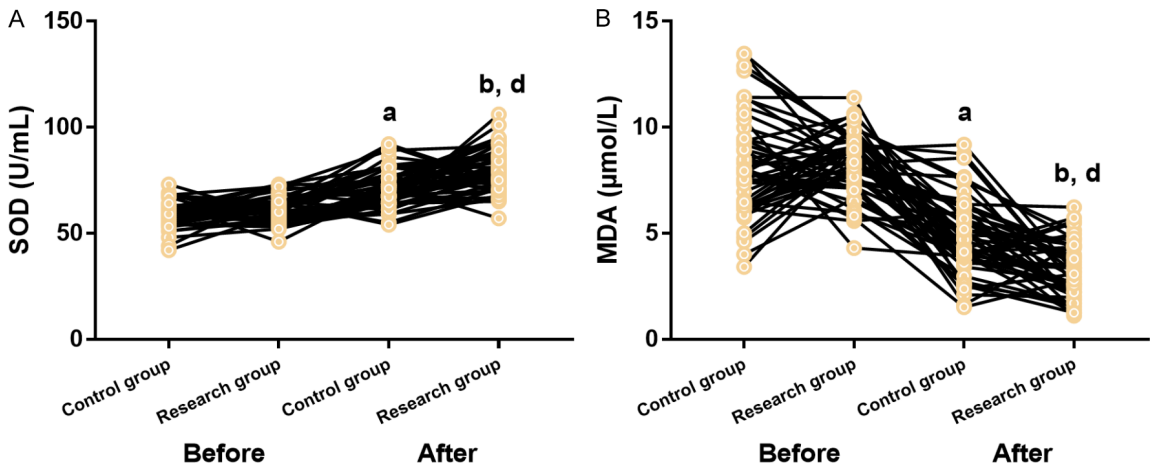

Figure 3. Comparison of oxidative stress markers. A. SOD measurements pre- and post-intervention. B. MDA in control and research groups. Note: SOD, superoxide dismutase; MDA, malondialdehyde. [a]P<0.05 and [b]P<0.01 relative to pre-treatment values; [d]P<0.05 versus the control cohort.

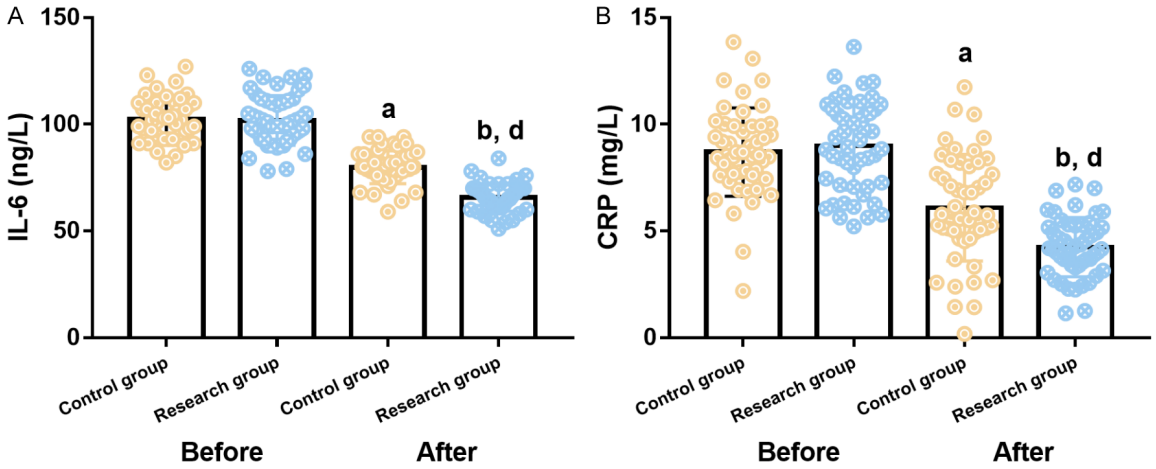

Figure 4. Intergroup analysis of inflammatory markers. A. IL-6 measurements for control and research groups. B. Comparison of CRP values across the two groups. Note: IL-6, interleukin-6; CRP, C-reactive protein. [a]P<0.05, [b]P<0.01 *vs.* pre-treatment; [d]P<0.05 *vs.* control group.

observed in the research group (P<0.05; **Figure 5**).

Therapeutic efficacy across the research groups

The research group had a total effective rate of 94.00%, higher compared to 76.00% in the control group (P<0.05; **Table 3**).

Safety outcomes in the two treatment groups

Analyzing adverse reactions (palpitations, nausea, fatigue, and dizziness), we found only 1 case each of palpitations and nausea in the research group, resulting in an overall incidence of 4.00%. The control group exhibited two cases of palpitation, three of nausea, two of fatigue, and one case of dizziness, with a total incidence of 16.00%. The inter-group comparison revealed an evidently lower overall adverse event incidence in the research group (P<0.05; **Table 4**).

Discussion

CHD is a major contributor to global morbidity and mortality. If complicated with HF, it will further increase the difficulty and complexity of treatment, which is not conducive to the improvement of patient prognosis [18, 19]. In view of the poor treatment effect of CHD com-

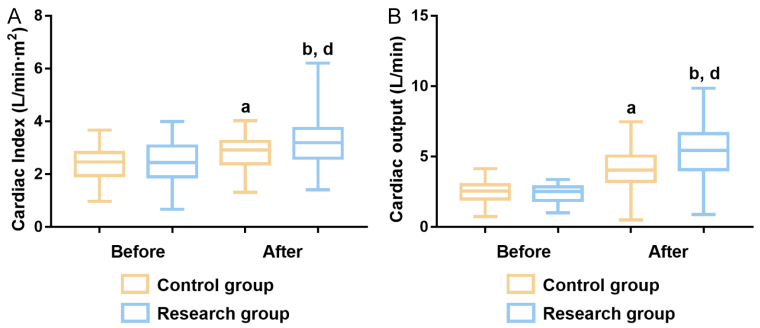

Figure 5. Hemodynamics of the two patient groups. A. Cardiac index measurements before and after treatment in both groups. B. Cardiac output in control vs. research group. Note: [a]P<0.05, [b]P<0.01 *vs.* pre-treatment; [d]P<0.05 *vs.* control group.

Table 3. Comparative analysis of clinical outcomes

Indicators	Control group (n=50)	Research group (n=50)	χ^2	P
Markedly effective	23 (46.00)	35 (70.00)		
Effective	15 (30.00)	12 (24.00)		
Ineffective	12 (24.00)	3 (6.00)		
Overall effectiveness	38 (76.00)	47 (94.00)	6.353	0.012

Table 4. Safety evaluation between groups

Indicators	Control group (n=50)	Research group (n=50)	χ^2	P
Palpitations	2 (4.00)	1 (2.00)		
Nausea	3 (6.00)	1 (2.00)		
Fatigue	2 (4.00)	0 (0.00)		
Dizziness	1 (2.00)	0 (0.00)		
Total	8 (16.00)	2 (4.00)	4.000	0.046

plicated with HF, the drug treatment scheme guided by the patient's condition adjustment and optimization guidelines may be more conducive to the improvement of curative effect [20]. Therefore, this study mainly verifies the clinical effect of metoprolol + spironolactone in CHD + HF treatment, aiming to provide more useful clinical reference for the treatment of such patients. Our data indicated more pronounced post-intervention LVESd and LVEDd reductions under metoprolol + spironolactone therapy than with sole-spironolactone treatment, as well as a greater rise in LVEF. These results suggest the combined therapy's positive effects on cardiac function. Furthermore, more patients in the research group achieved NYHA grade I/II and fewer had grade III/IV, indicating the ability of the coadministration to ameliorate fatigue, dyspnea, palpitations, and angina. Spironolactone's cardioprotection is partly attributed to its improvement of LV hemodynamics, ventricular remodeling, and myocardial function [21]. In the study of Taheri et al. [22], it was also officially stated that spironolactone has a certain improvement effect on cardiac function in patients with chronic hemodialysis, and can reduce LV mass without causing significant hyperkalemia. Similarly, literature has indicated metoprolol-mediated cardioprotection via cardiac function enhancement and cardiac metabolism regulation in streptozotocin-induced diabetic rats [23]. Moreover, in obstructive hypertrophic cardiomyopathy treatment, metoprolol contributed to a lower proportion of NYHA grade ≥III cases compared to placebo (14% vs. 38%) [24], supporting our results.

Metoprolol + spironolactone was proven to be more effective than spironolactone alone in normalizing BNP, evidenced by a more evident decrease in its levels in the research group post-treatment. BNP is mainly synthesized and secreted in LV myocytes, which can reflect the ventricular pressure overload. At the same time, its abnormal high expression is closely related to HF severity and can be an independent risk factor affecting HF patients' prognoses [25, 26]. Spironolactone has been reported to reduce BNP in HF patients with reduced ejection fraction [27], supporting our findings. Its effective downregulation of BNP may be related to its reduction of water and sodium retention, which helps to improve LV filling pressure as well as LV remodeling [28]. Consistently, Hara et al. [29] also reported that metoprolol for dilated cardiomyopathy significantly down-regulated BNP and LV dimensions at end diastole and end systole. Additionally, the combined therapy better alleviated oxidative stress and inflammation while improving hemodynamics in CHD-HF patients. This may be related to the fact that metoprolol

itself has antioxidant efficacy, and its combination with spironolactone can further enhance antioxidant activity, thereby reducing oxidative stress. Spironolactone's anti-inflammatory mechanism may be related to its inhibition of pro-inflammatory monocyte marker expression [30]. In rat experiments [31], spironolactone reduced cardiac hypertrophy and oxidative stress, supporting our data. In CHD-HF patients managed by metoprolol + spironolactone [32], Jiang et al. reported decreased CRP and improved cardiac index/output than metoprolol-treated cases, reaffirming our observations.

The research group further showed superior overall efficacy than controls (94.00% vs. 76.00%), underscoring enhanced efficacy by metoprolol + spironolactone. Only one case each of palpitations and nausea was found in the research group, demonstrating a markedly lower overall incidence than controls (three cases of nausea, two of palpitations, two of fatigue, and one of dizziness). Hence, the combination therapy has a favorable safety profile. In elderly HF patients with degenerative valvular heart disease, metoprolol + torasemide similarly enhanced cardiac performance and decreased N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, while exhibiting satisfactory safety [33]. In unstable angina, reduced adverse cardiovascular events and suppressed inflammation with metoprolol were also noted by Zhang et al. [34], echoing our results.

In conclusion, metoprolol + spironolactone for CHD + HF management enhanced cardiac function, accelerated symptomatic relief, attenuated disease progression, normalized BNP, and improved oxidative, inflammatory, and hemodynamic parameters. Compared with spironolactone monotherapy, this regimen has superior efficacy and good safety, and is a promising therapeutic strategy that is worthy of wider clinical adoption. Our findings reinforce the clinical value of combining established cardiovascular agents with complementary mechanisms. Looking forward, the exploration of novel therapeutic targets remains crucial. For instance, emerging research highlights the sphingosine 1-phosphate receptor 3 (S1PR3) signaling pathway as a key regulator in cardiac ischemia, fibrosis, and inflammation-processes central to CHD and HF progression. Modulators of S1PR3, such as fingolimod, have shown cardioprotective potential in preclinical and early clinical studies [35]. Future investigations comparing or combining such targeted approaches with conventional regimens like metoprolol-spironolactone may further optimize outcomes for patients with complex cardiovascular comorbidities.

Disclosure of conflict of interest

None.

Address correspondence to: Yansha Zhao, Department of Cardiovascular Medicine, Affiliated Hospital of Hebei University, 212 Yuhua East Road, Baoding 071000, Hebei, China. Tel: +86-0312-5983822; E-mail: m17334096025@163.com

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