ORIGINAL RESEARCH

The Impact of Glucocorticoid Therapy on Guideline-Directed Medical Treatment Titration in Patients Hospitalized for Heart Failure with Low Blood Pressure: A Retrospective Study

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Background: Positive inotropic and renal protective actions of glucocorticoids have been observed clinically. Therefore, glucocorticoids may be used in patients with heart failure and low blood pressure (HF-LBP).

Methods: The medical records of 144 consecutive patients with HF-LBP who received glucocorticoids as an adjunctive treatment to facilitate the up-titration of β-blocker and angiotensin-converting enzyme inhibitor were reviewed.

Results: After four weeks of treatment, the metoprolol and captopril (or equivalent) dosages were progressively and consistently increased from 25 (interquartile range [IQR] = 12.5–75 mg/day) to 100 mg/day (IQR = 50–178.8 mg/day) and from 0 (IQR = 0–25 mg/day) to 12.5 mg/day (IQR = 0–50 mg/day), respectively. There was a remarkable beneficial hemodynamic response to the glucocorticoid treatment signified by an increase in blood pressure and decrease in heart rate. The average heart rate decreased by 6 beat per minute (bpm) (0.5–16 bpm), and the mean arterial blood pressure increased from 74.06 ± 7.81 to 78.85 ± 7.91 mmHg. We also observed an improvement in renal function and an increased diuretic response following glucocorticoid treatment. As a result, the left ventricular ejection fraction increased from $28.92 \pm 8.06\%$ to $33.86 \pm 8.76\%$, and the diuretic response increased from 776.7 mL/40 mg furosemide (IQR = 133.8–2000 mL) to 4000 mL/40 mg furosemide on day 28 (IQR = 2200–5925 mL).

Conclusion: The use of glucocorticoid treatment to maintain hemodynamic and renal functional targets when titrating guideline-directed medical treatment in patients with HF-LBP may be safe, effective, and feasible.

Keywords: cardiac output, β-blocker, angiotensin-converting enzyme inhibitor, diuretic response, left ventricular ejection, renal function

Introduction

Cardiac output (CO) is the primary driver of blood pressure (BP) and is closely linked to BP. Patients with heart failure and low BP (HF-LBP) have increased rates of in- and out-of-hospital mortality. There are two important features in the pathophysiology of hospitalized patients with HF-LBP, namely congestion and low CO. Patients with HF-LBP are more likely to exhibit high venous pressure and poor renal perfusion. The maintenance of BP and renal function during hospitalization is of paramount importance in this population because these factors are the major determinants of the ability to introduce and titrate life-saving agents,

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eg, β-blockers and angiotensin-converting enzyme (ACE) inhibitors.[1,2] Treatment strategies should therefore target the adjustment of abnormal hemodynamics and facilitate increases in CO by simultaneously improving cardiac and renal function.[3] The improvement of CO should not be achieved at the expense of a further decrease in BP (ie, coronary perfusion pressure), an increase in heart rate (HR; ie, myocardial oxygen demand), or a triggering of neurohormonal activation (ie, worsening of renal function [WRF]).[2,4] Therefore, the need still exists to develop an agent with inotropic properties that can safely improve CO without adversely affecting BP and HR or causing a WRF.[2]

As early as the 1970s, the positive inotropic actions of various glucocorticoids were clinically observed.[5,6] The 2013 American Heart Association/American College of Cardiology Foundation guidelines list "steroids" as common precipitants of acute decompensated heart failure.[7,8] Although there are a series of adverse effects, eg, facial and leg swelling, weight gain and hypertension have associated with the use of glucocorticoids. There is no direct evidence that sodium retention was aroused using glucocorticoids.[9] In recent years, many studies have shown that glucocorticoids are a safe and effective treatment for HF.[10–13] In the past decade, serial animal and clinical studies have shown that glucocorticoids can improve renal function and increase diuresis in patients with HF.[9,14–16] The feature of glucocorticoids that allows them exhibit inotropic effects without negatively affecting HR, BP, and renal function make them a potential agent for hospitalized patients with HF-LBP. In recent years, glucocorticoid treatment has been used as an adjunctive treatment for patients with HF-LBP to facilitate the titration of guideline-directed medical treatment (GDMT), ie, β-blockers and ACE inhibitors. Therefore, the aims of the current study are to describe the effectiveness of using glucocorticoids to maintain hemodynamic and renal functional targets when titrating GDMT.

Methods
Study Design and Population
We reviewed the medical records of consecutive patients admitted to our institute with a primary diagnosis of decompensated HF with LBP. These patients received glucocorticoid treatment as an adjunctive therapy to maintain hemodynamic and renal functional targets while undergoing the titration of GDMT to target doses of neurohumoral blockers between December 2006 and

September 2019. The hospital medical ethics committee approved the study protocol. Patients were included as follows: a previous diagnosis of HF with reduced ejection fraction, systolic BP <110 mmHg, and New York Heart Association functional class IV. Every effort was made to achieve tolerated GDMT target doses of neurohumoral blockers. Patients with dehydration, cardiogenic shock, acute coronary syndrome, anemia, autonomic nervous dysfunction, gastrointestinal bleeding, acute severe infection, or malignant tumors were excluded. Patients were divided into three BP groups according to their systolic BP, ie, systolic BP <90 mmHg (lower tertile BP group), 90–99 mmHg (medium tertile BP group), and 100–109 mmHg (upper tertile BP group).

Decongestive Treatment and GDMT Titration
The pharmacological treatment of all study patients was at the discretion of the attending physician. Pharmacological agents administered included diuretics, vasodilators, and inotropic drugs. Intravenous vasodilators were used in cases where the systolic arterial BP was >90 mmHg. In general, inotropic agents were considered for patients with congestive symptoms that remained unimproved despite adequate unloading. If there were no emerging contraindications (eg, renal dysfunction), the doses of neurohumoral blockers including β-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists were adjusted in cases of congestive symptom deterioration or hemodynamic intolerance. An up-titration of neurohumoral blockers was performed as tolerated and always following a standardized protocol after clinical (symptomatic) stabilization. The decision of whether to up-titrate the neurohumoral blockers was largely influenced by the diuretic response. In cases where there was concern regarding diuretic resistance, the priority for up-titration was given to β-blockers.[17] Down-titration of ACE inhibitors or ARBs was performed only in patients with symptomatic hypotension or obvious diuretic resistance and was not based on the arterial BP measurement. Beta-blockers and ACEI/ARB drugs were standardized by metoprolol tartrate and captopril.

Glucocorticoid Treatment
Prednisone (1 mg/kg/day, with a maximum dose of 60 mg/day) was administered for two weeks and then gradually decreased. For those with hepatic dysfunction, an

equivalent dose of intravenous methylprednisolone was given for five days and then switched to prednisone treatment.

Outcomes

The primary outcomes were changes in the dosages of β-blockers and ACEIs, ARBs, or ARNIs after four weeks of glucocorticoid treatment. The secondary outcomes were changes in the BP, HR, serum creatinine (SCr), diuretic response, and left ventricular ejection fraction (LVEF) after four weeks of glucocorticoid treatment. The diuretic response was defined as the 24-hour urine output per 40 mg furosemide (or equivalent).[18]

Statistical Analysis

All statistical analyses were conducted using IBM SPSS 23.0. Continuous variables are expressed as the mean ± standard deviation, and those that were normally distributed were analyzed using the repeated measures analysis of variance, and those that were not, were expressed as the median (interquartile range [IQR]) and were analyzed using the Mann–Whitney U-test. Continuous variables in LVEF were analyzed using paired T test. Comparison among groups (three BP groups according to their systolic BP) was carried out using 1-way analysis of variance for continuous variables (normally distributed), U-test for continuous variables (non-normally distributed or normally distributed with heterogeneity of variance) and the chi-square test for discrete variables. A two-tailed $P < 0.05$ was considered statistically significant.

Results
Study Population

A total of 144 patients with HF-LBP were included in the present analysis, and the study patients were likely to have nonischemic cardiomyopathy. The baseline characteristics of these patients are presented in Table 1. The LVEF of the patients with HF-LBP was relatively low and accompanied by a poor diuretic response. We found that patients with HF-LBP in the lower tertile BP group (<90 mmHg) tended to use more intravenous inotropic agents than patients in the other groups, but the remaining clinical characteristics were similar in all three groups. It means that the hypoperfusion like increased HR and renal insufficiency was mainly caused by intricate damage from HF (low CO) rather than hypotension itself.

GDMT Titration with Glucocorticoid Treatment

Figure 1A and B show the changes in the dosage of neurohumoral blockers at the time of admission and on days 7, 14 and 28. During the four-week treatment period, the metoprolol (or equivalent)[19] and captopril (or equivalent)[20] dosages were progressively and consistently increased from 25 (IQR = 12.5–75 mg/day) to 100 mg/day (IQR = 50–178.8 mg/day, $P < 0.05$; see Figure 1A) and from 0 (IQR = 0–25 mg/day) to 12.5 mg/day (IQR = 0–50 mg/day, $P < 0.05$; see Figure 1B), respectively.

Blood Pressure and Heart Rate Responses to Glucocorticoid Treatment

During the four-week treatment period, there was a remarkable beneficial hemodynamic response to the glucocorticoid treatment signified by an increase in BP and a decrease in heart rate. The mean systolic BP increased from 94.71 ± 8.35 to 103.3 ± 10.52 mmHg ($P < 0.05$; see Figure 1C), and the mean arterial BP increased from 74.06 ± 7.81 to 78.85 ± 7.91 mmHg ($P < 0.05$). The mean diastolic pressure was also remarkably increased (Figure 1D) . In addition, the heart rate decreased from 74.5 (IQR = 66–84.75 bpm) to 68 bpm (IQR = 60–74 bpm, $P < 0.05$; see Figure 1E). Notably, LVEF increased from 28.92 ± 8.06% to 33.86 ± 8.76% ($P < 0.05$; see Figure 1F).

Changes in Renal Function and Diuretic Response

With GDMT titration, there was a notable renal improvement and increased diuretic response in patients with HF-LBP. Urine volume increased from 1500 (IQR = 1020–1950 mL) to 2700 mL (IQR = 2100–3300 mL) on day seven after the administration of glucocorticoids ($P < 0.05$; see Figure 1G). The change in SCr was –0.08 mg/dl (IQR = −0.03 – –0.21 mg/dl) on day 7, –0.13 mg/dl (IQR = –0.01 – –0.26 mg/dl) on day 14, and –0.19 mg/dl (IQR = –0.06 – –0.34 mg/dl) on day 28 ($P < 0.05$; see Figure 1H). The diuretic response increased from 776.7 (IQR = 133.8–2000 mL) to 4000 mL/40 mg furosemide on day 28 (IQR = 2200–5925 mL/40 mg, $P < 0.05$; see Figure 1I).

Subgroup Analysis

The data showed that the effects of glucocorticoid treatment were consistent across the three subgroups (lower tertile BP group, medium tertile BP group and upper tertile

Table 1 Demographic and Clinical Characteristics of the Study Population Overall and Stratified by Systolic Blood Pressure Systolic Blood Pressure

	Total (n=144)	100mmHg≤BP<110mmHg (n=47)	90≤BP<100mmHg (n=62)	BP<90mmHg (n=35)	P value
Demographic characteristics					
Age	52.00 (38.25–65)	50.40±16.92	50.07±18.26	51.80±14.05	0.885
Gender					
Male	108(75.0)	39 (83.0)	45 (72.6)	24 (68.6)	0.278
Female	36 (25.0)	8 (17.0)	17 (27.4)	11 (31.4)	0.278
Etiology					
ICM	18 (12.4)	7 (14.9)	7 (11.4)	4 (11.3)	0.677
DCM	106 (73.6)	33 (70.2)	47 (75.8)	26 (74.3)	0.677
VHD	7 (4.9)	4 (8.5)	2 (3.2)	1 (2.9)	0.677
HCM	5 (3.5)	2 (4.3)	1 (1.6)	2 (5.7)	0.677
PPCM	3 (2.1)	0 (0.0)	2 (3.2)	1 (2.9)	0.677
Other Causes	5 (3.5)	1 (2.1)	3 (4.8)	1 (2.9)	0.677
SBP (mmHg)	94.49 (93.09–95.89)	103.51 (102.57–104.45)	94.24 (93.53–94.96)	82.80 (81.17–84.43)	0.000
DBP (mmHg)	63.40 (61.92–64.87)	66.77 (63.71–69.82)	64.47 (62.86–66.08)	56.97 (54.35–59.59)	0.000
HR	74.50 (66.00–82.00)	75.87±13.41	75.55±13.47	78.00±16.60	0.702
Diuretic response (mL/40mg furosemide)	776.7 (133.8–2000)	791.5 (582.3–1700)	1200 (400–3100)	785 (388.3–1988)	0.395
Laboratory Results					
BUN (mg/dl)	45.44 (34.2–65.57)	49.64 (34.26–77.71)	43.03 (32.27–56.97)	45.44 (36.36–68.03)	0.199
SCr (mg/dl)	1.03 (0.89–1.26)	1.05 (0.96–1.26)	1.02 (0.83–1.22)	1.06 (0.83–1.26)	0.240
Echocardiography					
LVEF (%)	28.92±8.059	29.85±8.681	28.26±7.756	28.83±7.812	0.601
LVED (mm)	70.50 (65.00–76.00)	72.00 (70.00–77.00)	69.00 (65.00–76.00)	69.00(62.00–76.00)	0.429
Medication					
β-blocks	121 (84.0)	36 (76.6)	54 (87.1)	31 (88.6)	0.234
ACEI/ARB/ARNI	59 (41.0)	18 (38.3)	26 (41.9)	15 (42.9)	0.898
Intravenous Inotrope	21 (14.6)	6 (12.8)	5 (8.1)	10 (28.6)	0.021
Loop Diuretic	140 (97.2)	45 (95.7)	61 (98.4)	34 (97.1)	0.707

Abbreviations: ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; VHD, valvular heart disease; HCM, hypertrophic cardiomyopathy; PPCM, peripartum cardiomyopathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BUN, blood urea nitrogen; SCr, serum creatinine; LVEF, left ventricular ejection fraction; LVED, left ventricular end-diastolic diameter; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI; angiotensin receptor neprilysin inhibitor.

BP group). (See Figure 2A–I). That's mean that glucocorticoid treatment is apply to three BP groups.

Adverse Events During the Glucocorticoid Treatment Period

There were 10 deaths (6.9%) during the GDMT titration period. However, the incidence of severe adverse events associated with glucocorticoid treatment is low.

Discussion

The major finding of this study is that following the administration of glucocorticoids as an adjunctive therapy, the goal of

consistent and progressive increases in GDMT dosages was achieved without adversely affecting the CO or causing WRF in patients with HF-LBP. This finding indicates that glucocorticoid treatment may be an option in such populations.

Data from the present study provide cardiac and renal insights into the safety and tolerability of glucocorticoid treatment in patients with HF-LBP. First, glucocorticoid therapy in patients with HF-LBP could increase BP (coronary perfusion pressure) without a compensatory increase in HR (myocardial oxygen demand). Second, glucocorticoid therapy in patients with HF-LBP could improve renal function and renal perfusion (glomerular filtration rate
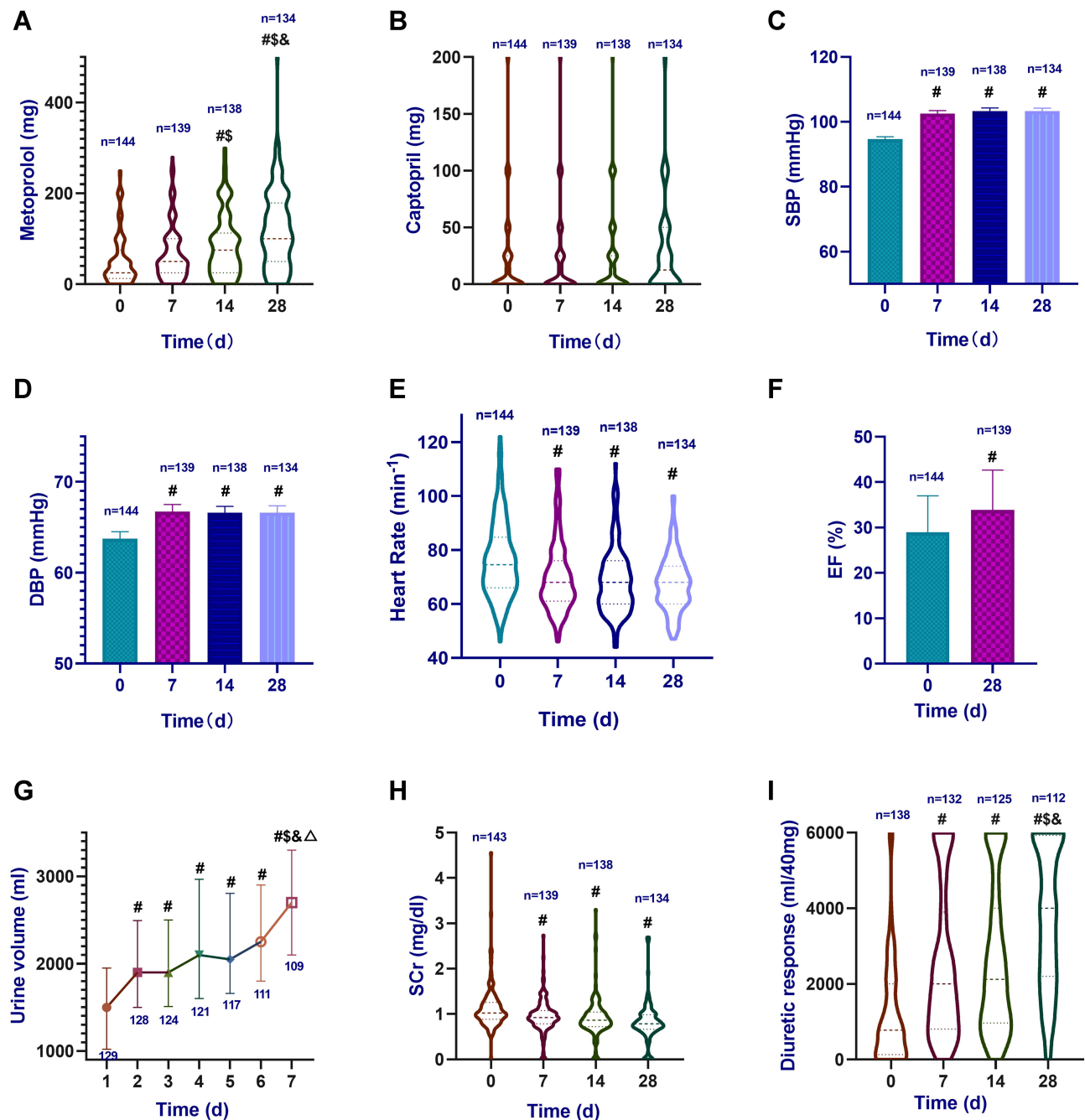
Figure 1 Clinical outcomes according to the use of glucocorticoids over 28 days among HF-LBP patients. (**A**) Change in dose of metoprolol; (**B**) change in dose of captopril; (**C**) change in SBP; (**D**) change in DBP; (**E**) change in heart rate; (**F**) change in EF; (**G**) change from baseline to the 7th day in urine volume; (**H**) change in SCr; (**I**) change in diuretic response. #Compared with baseline, $P < 0.05$; $Compared with the 7th day, $P < 0.05$; &Compared with the 14th day, $P < 0.05$; #Compared with the baseline, $P < 0.05$; $Compared with the 2nd day, $P < 0.05$; &Compared with the 3rd day, $P < 0.05$; *Compared with the 4th day, $P < 0.05$; △Compared with the 5th day, $P < 0.05$.

[GFR]). These favorable effects ultimately result in a significant improvement in cardiac function (measured by the LVEF) after one-month of GDMT titration.

Low systolic blood pressure is the Achilles's heel of HF. GDMT is the cornerstone of HF treatment and considerable evidence strongly suggested that β-blockers is

much safer and more beneficial to be initiated in HF patients.[21,22] However, hypotension and hypoperfusion in HF-LBP became an obstacle in prescription and titration of GDMT.[23] This greatly increased re-hospitalization and mortality (in-hospital and post-discharge) rate in patients with HF-LBP.[24] Currently available inotropes which used
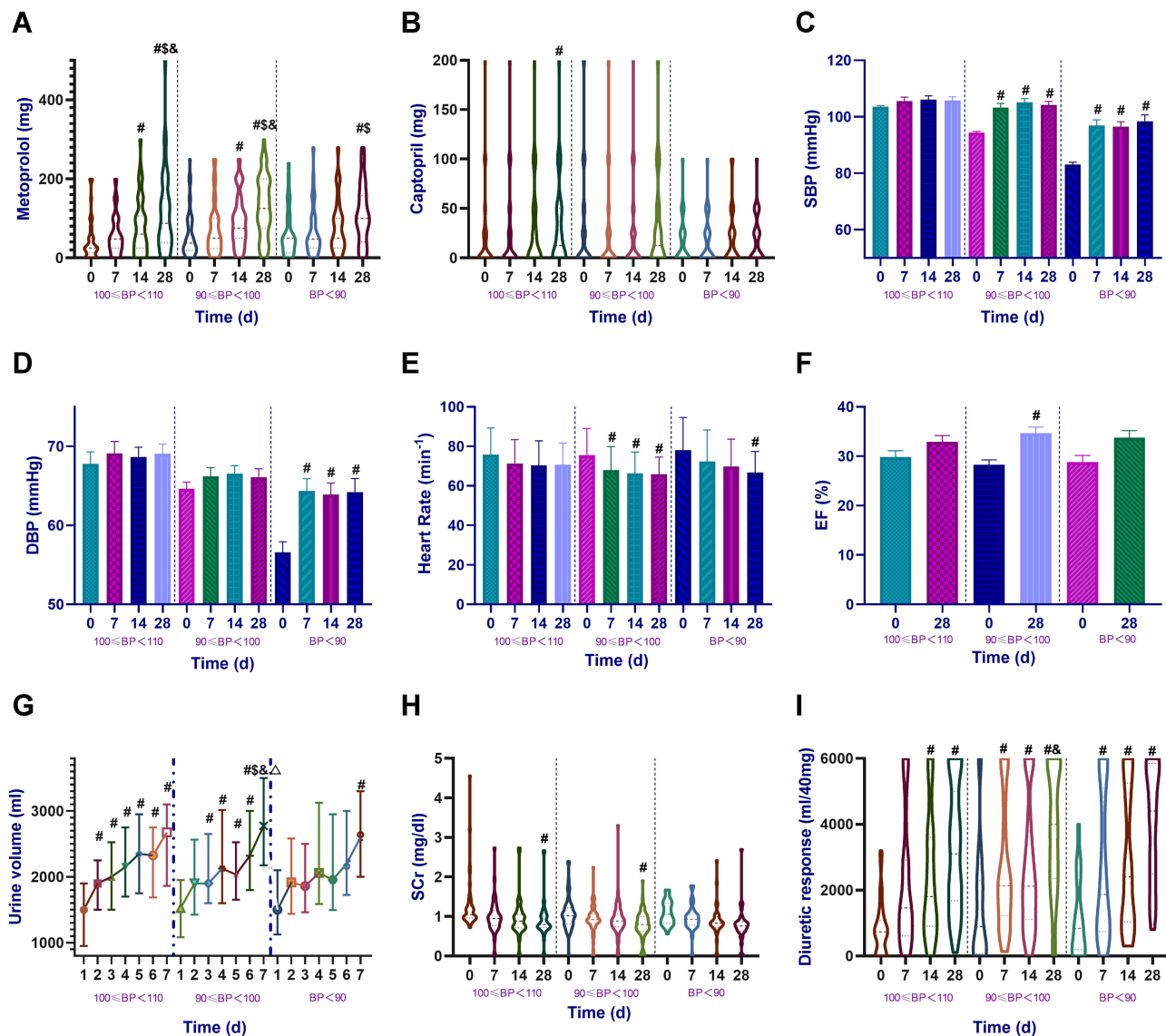
Figure 2 Subgroup analysis of clinical outcomes according to the use of glucocorticoids over 28 days among HF-LBP patients. (**A**) Change in dose of metoprolol; (**B**) change in dose of captopril; (**C**) change in SBP; (**D**) change in DBP; (**E**) change in heart rate; (**F**) change in EF; (**G**) change from baseline to the 7th day in urine volume; (**H**) change in SCr; (**I**) change in diuretic response. 100 ≤ BP < 110: upper tertile BP group; 90 ≤ BP < 100: medium tertile BP group; BP < 90: lower tertile BP group. #Compared with baseline, $P < 0.05$; $Compared with the 7th day, $P < 0.05$; &Compared with the 14th day, $P < 0.05$; #Compared with the baseline, $P < 0.05$; $Compared with the 2nd day, $P < 0.05$; &Compared with the 3rd day, $P < 0.05$; *Compared with the 4th day, $P < 0.05$; △Compared with the 5th day, $P < 0.05$.

to increase BP have been related to declines in BP, increase in heart rate, myocardial oxygen consumption and arrhythmias.[2]

The positive inotropic actions of glucocorticoids have been well documented clinically in patients without HF.[25,26] However, to the best of our knowledge, this is the first report to investigate the inotropic actions of glucocorticoids in patients with HF. This therapeutic strategy did not negatively impact the HR or BP while up-titrating GDMT dosages. Instead, a remarkable increase in BP and a reduction

in HR were observed, especially in patients in the lower tertile BP group. However, the mechanisms by which corticosteroids stimulate the cardiac muscle are not well understood. Animal studies using various disease models have indicated that multiple mechanisms may be involved in glucocorticoid-therapy-enhanced myocardial contractility. First, this influence may be indirectly mediated by the release and/ or potentiation of endogenous catecholamines.[27,28] Second, it could be a result of the upregulation of β-adrenergic receptors in the myocardium.[29] Third, it may be a consequence of

inflammatory suppression in HF.[6,30] Finally, the cardiovascular protective effects of glucocorticoids could be related to the endothelial nitric oxide synthase.[31–34]

Not only do glucocorticoids have positive inotropic actions but also renal protective effects. Newly emerging evidence from animal and clinical studies shows that glucocorticoids dilate the renal vasculature, potentiate renal responsiveness to diuretics, and increase the GFR.[15,16,35] Our findings in the present study are consistent with the previously published data. Glucocorticoids improved the renal function and increased the diuretic responsiveness in patients with HF-LBP. Although the underlying mechanisms are still not fully understood, the renal protective effects of glucocorticoids have been studied over the past decades. Gene regulation may play a critical role in the renal protective actions induced by glucocorticoids.[36,37] First, glucocorticoids can improve renal responsiveness to natriuretic peptides by upregulating the expression of natriuretic peptide receptor-A in the inner medullary collecting duct cells, thereby exerting a potent diuretic effect in decompensated HF.[14,36,38,39] Second, glucocorticoids can reduce vasopressin production while downregulating the expression of arginine vasopressin receptors in the kidneys.[30,40–42] Third, glucocorticoids increase renal blood flow and GFR by increasing the production of renal prostaglandin, nitric oxide, and dopamine.[32,43–45] Finally, the anti-inflammatory effects of glucocorticoids may also play a role in cardiorenal dysfunction.[30,46]

The main limitation of this retrospective study was the lack of randomization and a control group and the potential for variability in treatment. Indeed, although management decisions were enforced by a standardized protocol, decisions were ultimately made by the treating physician. In addition, this was a single-center study in a Chinese, experienced tertiary care center caring for patients with advanced heart failure. Caution should be taken when extrapolating these findings to other clinical settings. Finally, no invasive hemodynamic data were available pre- or post-titration with the GDMT agent. Therefore, we could not directly assess the impact of glucocorticoids on CO in such patients.

Conclusion

The results of our study indicate that the use of glucocorticoid treatment to maintain hemodynamic and renal functional targets when titrating GDMT in patients with HF-LBP may be safe, effective, and feasible. However, further investigation using randomized clinical trials is warranted.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of First Affiliated Hospital of Hebei Medical University. This study was conducted in accordance with the declaration of Helsinki. This study was retrospective and did not require informed consent of patients.

Disclosure

The authors declare that they have no competing interests.

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