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RESEARCH ARTICLE

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The comparative effects of sacubitril/valsartan versus enalapril on pulmonary hypertension due to heart failure with a reduced ejection fraction

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Abstract

The purpose of this study was to investigate the effects of sacubitril/valsartan on right ventricular (RV) function in patients with pulmonary hypertension (PH) due to heart failure with reduced ejection fraction (HFrEF). We prospectively enrolled patients with HFrEF-induced PH admitted to the Department of Cardiology between August 2018 and December 2019. Patients were randomized to receive oral treatment with sacubitril/valsartan or enalapril. Epidemiological data were recorded before treatment. Echocardiography was performed at admission and 6 months of follow-up, and all parameters were compared. Major adverse cardiac events (MACEs) were compared between baseline and 6 months follow-up. There were no significant differences in the baseline characteristics between the two groups. After 6 months of treatment, both treatment groups improved the following parameters from baseline (mean ± SD): left atrium, left ventricle, the left ventricular ejection function (LVEF), RV systolic function (the tricuspid annular plane systolic excursion [TAPSE], the systolic pulmonary artery pressure [sPAP], and TAPSE/sPAP). After 6 months, sacubitril/valsartan improved significantly the following parameters compared with enalapril (all $p < 0.05$): LVEF (47.07 ± 6.93% vs. 43.47 ± 7.95%); TAPSE (15.33 ± 1.31 vs. 14.78 ± 1.36 mm); sPAP (36.76 ± 14.32 vs. 42.26 ± 12.07 mmHg); and TAPSE/sPAP ratio (0.50 ± 0.23 vs. 0.39 ± 0.14), respectively. There was no difference in readmissions due to recurrent heart failure. Sacubitril/valsartan seems to provide more beneficial effects among patients with HFrEF-induced PH to improve RV function, along with a decrease in pulmonary pressure.

KEYWORDS
heart failure with reduced ejection fraction, PH-LHD, right ventricle, sacubitril/valsartan, TAPSE/sPAP

INTRODUCTION

Pulmonary hypertension (PH) is a hemodynamic disorder defined by unusually high pulmonary artery pressure (PAP) that can occur in numerous diseases and clinical situations. The causes of PH are classified into five major groups: arterial, due to left heart disease, due to lung disease and/or hypoxemia, and chronic thromboembolic, with unclear and/or multifactorial mechanisms.[1] PH is a life-threatening condition associated with increased mortality regardless of the classification and underlying etiology.[2] Globally, PH has an estimated prevalence of 1%, increasing to 10% in those aged 65 years and older,[3] The vast majority (almost 75%) of PH cases are caused by chronic left heart dysfunction (PH-LHD)[4,5] Left heart failure (LHF) is historically defined as a clinical syndrome caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output with elevated filling pressures at rest or during exercise or stress.[6] PH-LHD inexorably leads to right ventricular (RV) dysfunction, which has an additional detrimental effect on clinical status and outcomes.[7,8] The 12-month mortality for patients with PH-LHD may be as high as 32%.[9]

In patients with heart failure with reduced ejection fraction (HFrEF), the presence of PH (PH-LHD) has a significant impact on their prognosis. RV–PA coupling assessed by measuring the tricuspid annular plane systolic excursion (TAPSE)/systolic PAP (sPAP) ratio has been recently proposed as an early marker of RV dysfunction in patients with HFrEF,[10] the TAPSE/sPAP ratio has been proposed as the best echocardiographic method to evaluate it. Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, has been shown to reduce the risk of cardiovascular death or heart failure hospitalization and improve symptoms among patients with chronic HFrEF,[11] and sacubitril/valsartan can improve the RV–PA coupling.[10] However, only a few studies have evaluated the effects of sacubitril/valsartan on RV function. The purpose of this study was to investigate the effects of sacubitril/valsartan on RV function in patients of HFrEF with PH.

METHODS

We prospectively enrolled patients with PH due to HFrEF in the Department of Cardiology at our University and the Department of Cardiology at our Hospital from August 2018 to December 2019. In this study, HFrEF-induced PH was defined by echocardiography as having an EF of less than 40% and estimated sPAP more than 50 mmHg, and HFrEF-induced PH was considered to be present. The initial dose was determined according to blood pressure level and titrated gradually to sacubitril/valsartan 50 mg twice a day and enalapril 10 mg once a day. Other drugs including β-blockers, aldosterone receptor antagonists, diuretics, digitalis, and vasodilators were administered according to current guidelines. RV–PA coupling, estimated as the TAPSE/sPAP ratio values, was detected at the beginning of the sacubitril/valsartan therapy, and those measured at half a year after the initiation of therapy were evaluated. Epidemiological data on age, sex, and previous treatment were recorded; heart rate, blood pressure, 6- min walking distance (6MWD), and levels of N-terminal probrain natriuretic peptide (NT-proBNP) were recorded and compared before and after treatment. Echocardiography was performed at the beginning of treatment and 6 months after treatment. A complete echocardiographic examination was performed in the echocardiography laboratory by an experienced and skilled cardiologist. The primary endpoint was defined as the RV function, which was measured as the value of TAPSE and TAPSE/sPAP. The second endpoint was defined as the incidence of major adverse cardiac events (MACEs).

Inclusion criteria

The inclusion criteria included patients with estimated tricuspid peak velocity >3.4 m/s[12] and/or pulmonary systolic pressure >50 mmHg, which was determined using Doppler echocardiography.[13]

Exclusion criteria

The exclusion criteria included patients with hypersensitivity against sacubitril/valsartan or any of its metabolites, severe renal failure (creatinine >2.5 mg/dl), moderate or severe liver disease (i.e., a Child–Pugh score ≥7), severe chronic obstructive pulmonary disease (i.e., Global Initiative for Chronic Obstructive Lung Disease class ≥3), systolic blood pressure <85 mmHg, acute myocardial infarction, prior heart surgery with pericardial incision, and prior pulmonary embolism.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 25.0; IBM). Continuous data were presented as mean ± standard deviation (SD), while categorical data were expressed as number (percentage of patients). Comparisons of continuous variables were

made using the independent-samples T test, and χ^2 test or Fisher's exact test for categorical data. $p < 0.05$ was considered to be statistically significant.

RESULTS

From August 2018 to December 2019, 113 patients with PH due to HFrEF were admitted to our department. The following patients were excluded: two refused to participate in the study, four had severe renal disease, three had moderate or severe liver disease, five had moderate or severe chronic obstructive pulmonary disease, and two had an acute myocardial infarction. The remaining 97 patients were enrolled in the study and randomly assigned to either the sacubitril/valsartan group (52 patients) or the enalapril group (45 patients).

Baseline characteristics between the two groups

The baseline characteristics are shown in Table 1. There were no significant differences between the two groups in epidemiological data, the cause of HFrEF-induced PH, results of laboratory examinations, and medical treatments (all $p > 0.05$).

Changes in RV function detected by echocardiography

The LA, LV, left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), stroke volume (SV), left ventricular ejection function (LVEF), TAPSE, sPAP, TAPSE/sPAP, and PA diameter and aortic diameter ratio (PA/AO) were similar between the two groups before treatment ($p > 0.05$). After 6 months of treatment using sacubitril/valsartan or enalapril, the LVEF ($47.07 \pm 6.93\%$ vs. $43.47 \pm 7.95\%$, $p < 0.05$), the TAPSE (15.33 ± 1.31 vs. 14.78 ± 1.36 mm, $p < 0.05$), and the TAPSE/sPAP (0.50 ± 0.23 vs. 0.39 ± 0.14, $p < 0.05$) were significantly increased in the sacubitril/valsartan group compared with the enalapril group; the diameter of LA (40.40 ± 3.72 vs. 42.18 ± 3.92 mm, $p < 0.05$), the diameter of LV (50.98 ± 4.23 vs. 52.93 ± 5.01 mm, $p < 0.05$), the LVESV (80.60 ± 23.20 vs. 94.69 ± 44.28 ml, $p < 0.05$), the level of sPAP (36.76 ± 14.32 vs. 42.26 ± 12.07 mmHg, $p < 0.05$), and the value of PA/AO (0.76 ± 0.07 vs. 0.80 ± 0.05, $p < 0.05$) were significantly decreased in the sacubitril/valsartan group compared with the enalapril group. All of the data are shown in Table 2.

Clinical data after treatment and at 6 months of follow-up

The NT-proBNP, 6MWD, heart rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) levels were similar between the two groups before treatment ($p > 0.05$). After 6 months of treatment using sacubitril/valsartan and enalapril, the levels of NT-proBNP (458.46 ± 459.30 vs. 673.14 ± 556.54 pg/ml, $p < 0.05$) and the level of DBP (67.19 ± 5.52 vs. 71.24 ± 7.27 mmHg, $p < 0.05$) were significantly decreased in the sacubitril/valsartan group compared with the enalapril group, while the level of 6MWD (429.23 ± 87.92 vs. 394.33 ± 71.02 m, $p < 0.05$) was significantly increased in the sacubitril/valsartan group compared with the enalapril group. All of the data are shown in Table 3.

After 6 months of treatment, the levels of NT-proBNP, heart rate, SBP, and DBP were significantly decreased in the enalapril group ($p < 0.05$), and the level of 6MWD was significantly increased in the enalapril group ($p < 0.05$); the levels of NT-proBNP, heart rate, SBP, and DBP were significantly decreased in sacubitril/valsartan group (p all <0.05) and the level of 6MWD was significantly increased in sacubitril/valsartan group ($p < 0.05$).

Clinical data after treatment and at 6 months of follow-up

After treatment, there were no significant differences in death and hospital duration. After 6 months of follow-up, there was no significance in readmission due to recurrent heart failure. The data are shown in Table 4.

Safety evaluation

Sacubitril/valsartan 50 mg was well tolerated well. During the trial, only five patients developed significant hypotension after starting to take sacubitril/valsartan, and their blood pressure was stable after several days of medication adjustment and cardiac function stabilization.

DISCUSSION

PH is a severe complication in patients affected by chronic left-sided heart failure. It dramatically impacts their exercise capacity, quality of life, and survival. PH in chronic left-sided heart failure is not merely caused by a backward transmission of pressures, but it is a complex process that involves atrial function, inflammation, and vasoconstriction. Once PVR increases and the impairment of PA compliance

TABLE 1 Comparison of baseline characteristics between the two groups

Variable	Enalapril group ($n = 45$)	Sacubitril/valsartan group ($n = 52$)	p value
Age (years)	66.71 ± 10.42	68.65 ± 10.48	0.364
Female, *n* (%)	25 (55.56)	29 (55.77)	0.983
Weight (kg)	73.27 ± 10.15	70.95 ± 8.62	0.227
BMI (kg/m^2)	25.54 ± 3.30	24.66 ± 2.44	0.135
SBP (mmHg)	128.67 ± 16.62	133.58 ± 15.27	0.133
DBP (mmHg)	80.09 ± 13.10	75.73 ± 9.61	0.063
HR (beats/min)	84.71 ± 20.32	79.35 ± 12.00	0.111
Cause			
Ischemia, *n* (%)	29 (64.44)	35 (67.31)	0.767
Nonischemia, *n* (%)	16 (35.56)	17 (32.69)	0.767
Hypertension, *n* (%)	27 (60.00)	32 (61.54)	0.877
Diabetes (*n*, %)	25 (55.56)	34 (65.38)	0.323
NYHA classification			
NYHA III, *n* (%)	21 (46.67)	28 (53.85)	0.481
NYHA IV, *n* (%)	24 (53.33)	24 (46.15)	0.481
Laboratory examination			
BUN (mmol/L)	7.15 ± 2.43	6.33 ± 1.77	0.056
SCr (μmol/L)	74.73 ± 13.23	76.38 ± 12.38	0.526
UA (μmol/L)	370.09 ± 102.76	349.41 ± 69.98	0.244
Glu (mmol/L)	6.20 ± 1.54	6.09 ± 1.46	0.716
NT-proBNP (pg/ml)	2814.49 ± 1356.44	2899.27 ± 1136.33	0.738
Medicines			
Aspirin, *n* (%)	27 (60.00)	33 (63.46)	0.726
Clopidogrel/ticagrelor, *n* %)	24 (53.33)	28 (53.85)	0.960
Statins, *n* (%)	25 (55.56)	32 (61.54)	0.474
Beta-blocker, *n* (%)	39 (86.67)	47 (90.38)	0.565
Diuretics, *n* (%)	40 (88.89)	48 (92.31)	0.563
Spirolactone, *n* (%)	42 (93.33)	50 (96.15)	0.531
Digitalis, *n* (%)	18 (40.00)	21 (40.38)	0.969
Nitrate, *n* (%)	27 (60.00)	30 (57.69)	0.818
Oral anticoagulants, *n* (%)	16 (35.56)	18 (34.62)	0.923

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; Glu, glucose; HR, heart rate; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SCr, serum creatinine; UA, urea acid.

appears, the RA attempts to compensate for the increased afterload. When this compensatory mechanism fails, RV dilatation and systolic dysfunction occur, leading to right heart failure and death.[14] In patients with HFrEF, an increase in the left atrial (LA) pressure and a reduction in LA compliance[15,16] leads to LA remodeling (increase in LA size, impaired LA contractility, and interstitial fibrosis), resulting in an increase in LA stiffness, which is a major determinant of PH.[17] In this study, we investigated the comparative effects of sacubitril/valsartan versus enalapril on RV function in patients with HFrEF-induced PH, and we found that although both drug regimens improved several cardiac parameters, sacubitril/valsartan improved RV function, sPAP, NT-proBNP, and 6MWD significantly more than enalapril.

TABLE 2 Changes in the echocardiographic parameters during follow-up

Variable	Group	Baseline	6 months follow-up	*p* value
LA (mm)	Enalapril group	49.27 ± 2.96	42.18 ± 3.92	0.000
	Sacubitril/valsartan group	49.37 ± 3.31	40.40 ± 3.72*	0.000
LV (mm)	Enalapril group	62.24 ± 5.10	52.93 ± 5.01	0.000
	Sacubitril/valsartan group	62.25 ± 5.86	50.98 ± 4.23*	0.000
LVEDV (ml)	Enalapril group	173.11 ± 61.64	162.51 ± 56.06	0.396
	Sacubitril/valsartan group	173.60 ± 45.76	152.06 ± 37.24	0.010
LVESV (ml)	Enalapril group	113.51 ± 48.70	94.69 ± 44.28	0.058
	Sacubitril/valsartan group	112.21 ± 32.19	80.60 ± 23.20*	0.000
SV (ml)	Enalapril group	59.76 ± 15.91	67.82 ± 15.75	0.018
	Sacubitril/valsartan group	62.10 ± 15.20	71.46 ± 19.33	0.007
LVEF (%)	Enalapril group	35.18 ± 4.73	43.47 ± 7.95	0.000
	Sacubitril/valsartan group	35.80 ± 3.94	47.07 ± 6.93*	0.000
TAPSE (mm)	Enalapril group	13.22 ± 1.40	14.78 ± 1.36	0.000
	Sacubitril/valsartan group	13.40 ± 1.61	15.33 ± 1.31*	0.000
sPAP (mmHg)	Enalapril group	57.71 ± 6.32	42.26 ± 12.07	0.000
	Sacubitril/valsartan group	57.75 ± 8.11	36.76 ± 14.32*	0.000
TAPSE/sPAP	Enalapril group	0.23 ± 0.03	0.39 ± 0.14	0.000
	Sacubitril/valsartan group	0.24 ± 0.04	0.50 ± 0.23*	0.000
PA/AO	Enalapril group	0.81 ± 0.06	0.80 ± 0.05	0.380
	Sacubitril/valsartan group	0.79 ± 0.06	0.76 ± 0.07*	0.033

Abbreviations: LA, left atrium; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; PA/AO, PA diameter and aortic diameter ratio; sPAP, systolic pulmonary artery pressure; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion.

*$p < 0.05$ compared with the enalapril group.

TABLE 3 Changes in the NT-proBNP, 6MWD, heart rate, SBP, and DBP levels at 6 months of follow-up

Variable	Group	Baseline	6 months follow-up	*p* value
NT-proBNP (pg/ml)	Enalapril group	2814.49 ± 1356.44	673.14 ± 556.54	0.000
	Sacubitril/valsartan group	2899.27 ± 1136.33	458.46 ± 459.30*	0.000
6MWD (m)	Enalapril group	214.80 ± 94.37	394.33 ± 71.02	0.000
	Sacubitril/valsartan group	201.90 ± 95.43	429.23 ± 87.92*	0.000
HR (beats/min)	Enalapril group	84.71 ± 20.32	67.56 ± 7.00	0.000
	Sacubitril/valsartan group	79.35 ± 12.00	66.52 ± 5.45	0.000
SBP (mmHg)	Enalapril group	128.67 ± 16.62	122.38 ± 9.49	0.030
	Sacubitril/valsartan group	133.58 ± 15.27	122.37 ± 9.69	0.000
DBP (mmHg)	Enalapril group	80.09 ± 13.10	71.24 ± 7.27	0.000
	Sacubitril/valsartan group	75.73 ± 9.61	67.19 ± 5.52*	0.000

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; 6MWD, 6-min walking distance; NT-proBNP, N-terminal probrain natriuretic peptide; SBP, systolic blood pressure.

*$p < 0.05$ compared with the enalapril group. Enalapril group, $n = 44$ and sacubitril/valsartan group, $n = 51$.

TABLE 4 MACEs during 6 months of follow-up

Variable	Enalapril group ($n = 45$)	Sacubitril/valsartan group ($n = 52$)	p value
Death, n (%)	1 (2.22)	1 (1.92)	0.918
Hospitalization (days)	11.02 ± 2.60	10.75 ± 2.79	0.622
Readmission, n (%)	2 (4.44)	1 (1.92)	0.454

Abbreviation: MACE, major adverse cardiac events.

In this study, all medications were used according to current guidelines. There were no significant differences in the use of diuretics, digitalis, and nitrates between the two groups (Table 1). The 6-min walk test is widely used to assess the severity and prognosis of PH.[18] In patients with suspected PH, a decreased 6-min walk distance is due to compromised oxygen delivery, decreased cardiac reserve, and increased RV afterload.[18] In this study, the value of PA/AO in the sacubitril/valsartan group significantly decreased than that in the enalapril group. PA/AO and TAPSE can be used to assess the level of the heart and great vessels without the severity of the shunt in patients with PH.[19] Although age and body surface area may have a slight influence on TAPSE, TAPSE < 17 mm is highly suggestive of RV systolic dysfunction,[20] and <8 mm is often associated with severe RV dysfunction.

The presence of elevated SPAP is associated with a poor prognosis in HF.[21] In this study, after 6 months of treatment, sPAP significantly decreased, while TAPSE and TAPSE/sPAP significantly increased in the sacubitril/valsartan group compared with the enalapril group; there were no significant differences in death, hospital duration, and readmission due to recurrent heart failure between the two groups. TAPSE/sPAP has been shown to be associated with cardiac functional status and prognosis of HFrEF.[22,23] TAPSE/sPAP is a promising echocardiographic parameter that can help answer the question of how much cardiopulmonary reserve is consumed. A growing body of evidence suggests that this ratio provides more information than considering a single parameter, may contribute to the stratification of patient risk, and is associated with adverse clinical outcomes.[23,24] The TAPSE/sPAP ratio has important prognostic implications; in fact, a TAPSE/sPAP ratio <0.36 mm/mmHg identified patients with a high risk, irrespective of EF status.[25] Different studies obtained different TAPSE/sPAP cutoff values, which may be related to the selected target population, sample size, and other factors.

Due to the increase of LAVI and LA pressure, LA no longer acts as a barrier between left ventricular hypertension and pulmonary vessels, resulting in the passive transfer of left ventricular pressure to the pulmonary vascular tree,[26] leading to the increase of PAP, resulting in increased RV afterload and ventricular remodeling. Sacubitril/valsartan may prevent maladaptive RV remodeling in a pressure overload model via amelioration of RV pressure rise, hypertrophy, collagen, and myofiber reorientation, as well as tissue stiffening at both the tissue and myofiber level.[27] In addition to the direct effects on the RV, there is evidence showing that sacubitril/valsartan has an antiproliferative effect on cultured human PA smooth muscle cells (PA-SMCs) derived from patients with idiopathic PAH, an effect that is more pronounced in the presence of bosentan.[28] This effect on the pulmonary vasculature may, in part, explain the beneficial actions of this combination therapy. Sacubitril/valsartan can improve RV–PA coupling; this improvement is related to both an increase in the TAPSE and a reduction in the pulmonary arterial pressure, and the improvement in the TAPSE/sPAP ratio is independent of the LV reverse remodeling.[10] In contrast, this study shows that in patients with HFrEF, improvement in pulmonary arterial pressure is thought to be associated with the reversal of adverse left ventricular remodeling; this difference may be due to different target populations and different coexisting diseases.

Recently, in a pressure overload model of PH, sacubitril/valsartan, due to the combined natriuretic and vasodilator effects, prevents maladaptive RV remodeling via the amelioration of RV contractility and relaxation, reduction in RV afterload, and improvement in RV–PA coupling.[27] In this study, we included 97 HFrEF-induced PH patients and found that sacubitril/valsartan could reduce the size of the left heart and increase the systolic function of LV. At the same time, sacubitril/valsartan could reduce the preload and afterload of the right heart, reduce the pulmonary pressure, and increase the systolic function of the right ventricle (as TAPSE), which was consistent with the views of Correale et al.[29]

Although sacubitril/valsartan has useful effects in systolic LHF are well known, limited data are available on the utilization in right heart failure. In this study, sacubitril/valsartan improved the RV performance by acting on the RV contractility (indirectly estimated by TAPSE and S wave) and reducing the RV afterload (indirectly estimated by sPAP), with an improvement in the RV–PA coupling.[10] The present study suggests that sacubitril/valsartan is an effective therapy in the treatment of HFrEF-induced PH.

STUDY LIMITATION

First of all, this was a two-center study with a relatively small sample size of PH patients induced by HFrEF, and these results need to be further validated in larger multicenter clinical randomized controlled trials. Second, two-dimensional ultrasound was used in this study to assess PAP, and sPAP≥ 50 mmHg was adopted as the inclusion criteria to improve the accuracy of patients' diagnostic pH; if echocardiography is combined with a right heart catheterization, more reliable reference data can be obtained. In addition, our trial used a fixed dose of sacubitril/valsartan. The efficacy of different doses of sacubitril/valsartan needs to be further explored in future studies with larger sample sizes and different dose groups.

CONCLUSIONS

In HFrEF-induced PH patients, 6 months of sacubitril/valsartan therapy increased TAPSE, decreased sPAP, and improved RV–PA coupling and was more beneficial than enalapril.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

ETHICS STATEMENT

This study was conducted in accordance with the Declaration of Helsinki, all the patients provided written informed consent, and the study was approved by the local ethics committee.

AUTHOR CONTRIBUTIONS

Li-xin Zhang, Tao Ma, Yan-bo Wang, and Xin-shun Gu participated in the design, implementation, review, and modification of the paper. Ying Zhao, Li-guo Tian, Liang Di, Dan-dan Wang, Shang Gao, and Haiyan Wang participated in the whole process of data collection, search literature, statistical analysis, and article modification.

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