The Impact of Sacrubitril/Valsartan on Clinical Treatment and hs-cTnT and NT-ProBNP Serum Levels and the Left Ventricular Function in Patients with Chronic Heart Failure

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Summary
Chronic heart failure (CHF) seriously affects the quality of patients’ lives. Sacrubitril/valsartan is a combination angiotensin receptor-neprilysin inhibitor, a new therapeutic drug to treat CHF.

This study aims to observe the impact of sacrubitril/valsartan on clinical treatment and high-sensitivity cardiac troponin T (hs-cTnT), N-terminal pro-brain natriuretic peptide (NT-ProBNP) serum levels, the improvement of the left atrial diameter (LAD) and left ventricular end diastolic dimension (LVEDD), and the left ventricular ejection fraction (LVEF) in patients with CHF.

120 patients were randomly divided into a sacrubitril/valsartan group and a valsartan group, with 60 cases in each. Patients in the sacrubitril/valsartan group were administered sacrubitril/valsartan; while in the valsartan group, they were administered valsartan. The clinical effects, adverse reactions, and rehospitalization were observed eight weeks later, and hs-cTnT and NT-ProBNP serum levels and LAD, LVEDD, and LVEF were assayed.

There were 53 cases of positive effect in the sacrubitril/valsartan group and 42 in the valsartan group (P < 0.05). Eight participants demonstrated adverse reactions in the sacrubitril/valsartan group, while 17 in the control group (P < 0.05). Hs-cTnT and NT-ProBNP serum levels, the measurements of LAD, LVEDD, and LVEF in the sacrubitril/valsartan group before the treatments were (24.47 ± 7.54) pg/mL, (10,356.94 ± 5,447.68) pg/mL, (49.41 ± 5.22) mm, (68.06 ± 6.20) mm and (31.12 ± 6.65) %; in the valsartan group were (29.75 ± 10.03) pg/mL, (9,518.17 ± 5,905.17) pg/mL, (49.65 ± 4.91) mm, (67.06 ± 3.97) mm, and (30.41 ± 6.11) % (P > 0.05), while in the sacrubitril/valsartan group, the values decreased after the treatments to (17.92 ± 4.74) pg/mL, (3,881.59 ± 2,087.79) pg/mL, (42.18 ± 4.87) mm, (60.35 ± 7.12) mm, and (45.35 ± 4.49)%; in the valsartan group to (25.81 ± 7.36) pg/mL, (6,278.35 ± 2,643.11) pg/mL, (46.53 ± 4.80) mm, (64.51 ± 4.34) mm, and (36.47 ± 5.21) % (P < 0.05). There were significant differences within the same group, before and after treatments (P < 0.05).

Sacrubitril/valsartan treatment of patients with CHF improves their symptoms and is deserving of clinical application. This is also evident from significantly improved levels of serum hs-cTnT and NT-ProBNP and the left ventricular function.

Key words: LVEF

With the rise in the aging population, morbidity and mortality from chronic heart failure (CHF) is increasing, and with a five-year survival rate around 50%, it is a serious threat to human health.1,2) CHF is the terminal stage of most myocardial diseases. Such a condition results from various forms of cardiomyocyte injury, and it changes the structure of the cardiomyocyte, resulting in cardiac remodeling and eventually depresses the heart’s blood pumping function. Dyspnea, edema, and fatigue are the main characteristics of the clinical syndrome.3

Sacrubitril/valsartan was mentioned in the guidelines of the European Society of Cardiology (ESC) with regard to acute and chronic systolic heart failure for the first time in 2016. It is a combination of an angiotensin receptor blocker (valsartan) and a neprilysin inhibitor (sacrubitril). Developed by Novartis, it has been on the market in China since July 2017 as an innovative drug for the treat-
ment of CHF.4,5)

In our study, we compared treatment with sacrubitril/valsartan to that of valsartan, combined the general treatments with aldosterone antagonist and β-blocker, observed clinical effects, assayed the levels of hs-cTnT and NT-ProBNP in serum, and measured the value of LAD, LVEDD, and LVEF in order to figure out if sacrubitril/valsartan could improve levels of serum hs-cTnT and NT-ProBNP and the left ventricular function.

Methods

Patient population: 120 cases of CHF, diagnosed and treated initially by the heart center at People’s Hospital of Liaoning Province from September 2017 to March 2019, were selected. Based on the inclusion and exclusion criteria, they were divided into a sacrubitril/valsartan group and a valsartan group, with 60 cases in each. The underlying diseases and the reason of heart failure of the patients were in Table I. Baseline data were obtained from the patients before the treatments (Table I). The study was in accordance with the Declaration of Helsinki, approved by local ethics committee, and all patients were provided written informed consent.

Inclusion criteria were as follows: (1) aged > 60 years; (2) definite diagnosis of CHF (New York Heart Association (NYHA) Class II-IV, with LVEF ≤ 40%); (3) withdraw the use of angiotensin-converting enzyme (ACE) inhibitors for at least 36 hours; (4) no tumors or autoimmune diseases; and (5) signed informed consent for the treatments.

Exclusion criteria were as follows: (1) acute heart failure; (2) serious diseases of the liver, kidney or other important organs; (3) heart failure caused by anemic heart disease, cor pulmonale, hyperthyroid cardiopathy, congenital and idiopathic cardiomyopathy, valvular heart disease, congenital heart diseases, malignant tumor and acute myocardial infarction; (4) systolic blood pressure < 90 mmHg, heart rate < 55 beats/min, (5) hyperkalemia; (6) mental illness; (7) poor compliance; and (8) allergic or other adverse reaction to drugs used in this study.

Treatments: Before the start of this study, the medication status of ACE inhibitors or ARB more than 36 hours was in Table I. Based on their condition, general treatments such as β-blockers, aldosterone antagonists, digitalis, and loop diuretics were administered to all patients, as shown in the Table I. In addition to these general treatments, patients in the sacrubitril/valsartan group were given sacrubitril/valsartan orally, 50 mg, twice a day; while patients in the valsartan group were given valsartan orally, 80 mg, once a day.

Observed indicators: The clinical effects and any adverse reactions were observed 8 weeks later, levels of serum hs-cTnT and NT-ProBNP were assayed, and LAD, LVEDD, and LVEF were measured in both study groups. Clinical criteria for judging the treatments included the following: (1) a pronounced and remarkable effect on symptoms of dyspnea, edema, and no fatigue, cardiac function improved two classes or recovery to NYHA Class I; (2) obvious improvement of symptoms of dyspnea, edema, and fatigue, cardiac function improved one class but did not reach NYHA Class I; (3) no positive or negative effect on symptoms of dyspnea, edema and fatigue, no positive or negative change in cardiac function, which may need in-hospitalization. These criteria were noted as the classification titles “remarkable effect”, “effect,” and “no effect”, respectively. The incidence of adverse reactions was determined by angioedema, hypotension, hyperkalemia, and severe renal insufficiency. Patients were asked to record their blood pressure every day. Before and after the treatments, 4 mL blood was taken from all the patients in tubes with separating gel. The blood was incubated for 10 minutes and then centrifuged for 10 minutes at 3000 rpm. Concentrations of blood potassium and creatinine levels were detected by the ion-selective electrode method and enzymatic method, respectively. Levels of serum hs-cTnT and NT-ProBNP were detected by electrochemiluminescence. Also, the values of LAD and LVEDD were measured using cardiac color doppler ultrasound diagnostic system (CX50, Philips, Netherlands) before and after the treatment, and LVEF was calculated by corrected body surface area of all patients.

Statistical analysis: Measurement data were presented as a means ± SD, and the analysis of covariance (ANCOVA) and t-tests were used to analyze the differences between the two groups. Enumeration data were presented as ratios and chi-square test was used to analyze differences between the two groups. All the data were analyzed by using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Inc., Chicago, USA); P < 0.05 was considered statistically significant.

Results

Evaluating therapeutic effects, adverse reactions and rehospitalization: As shown in Table II, there were 53 cases of effect in the sacrubitril/valsartan group (remarkable effect 18 cases, effect 35 cases, while no effect seven cases), and 42 cases in the valsartan group (remarkable effect 4 cases, effect 38 cases, while no effect 18 cases). The positively effective rate of clinical treatments in the sacrubitril/valsartan group was 88.33%, compared to 70.00% in the valsartan group. This difference was statistically significant (P < 0.05). Eight participants (hypotension seven cases, severe renal insufficiency one case) exhibited adverse reactions in the sacrubitril/valsartan group, while there were 17 cases (hypotension seven cases, hyperkalemia three cases, severe renal insufficiency seven cases) in the valsartan group. The incidence rate of adverse reactions in the sacrubitril/valsartan group compared to the valsartan group was 13.33% and 28.33%, respectively; a difference that was also statistically significant (P < 0.05). Eight participants (cardiac function worsen six cases, acute myocardium infarction two cases, severe renal insufficiency one case, stroke zero cases) needed rehospitalization in the sacrubitril/valsartan group, while there were 17 cases (cardiac function worsen 15 cases, acute myocardium infarction one case, severe renal insufficiency seven cases, stroke 0 cases) in the valsartan group. The incidence rate of rehospitalization in the sacrubitril/valsartan group compared to the valsartan group was 13.33% and 28.33%, respectively; a difference that was also statis-
**Table I.** Baseline Data of the Patients in the Two Groups

| Variables                                 | Sacrubitil/valsartan group $(n = 60)$ | Valsartan group $(n = 60)$ | $P$ value |
|-------------------------------------------|--------------------------------------|---------------------------|-----------|
| Age, years                                | 70.53 ± 7.05                         | 70.00 ± 7.51              | 0.834     |
| Male, (%)                                 | 46 (76.67)                           | 42 (70.00)                | 0.409     |
| NYHA class, $n$ (%)                       |                                      |                           | 0.695     |
| II                                        | 11 (18.33)                           | 14 (23.33)                | 0.500     |
| III                                       | 25 (41.67)                           | 21 (35.00)                | 0.453     |
| IV                                        | 24 (40.00)                           | 25 (41.67)                | 0.853     |
| The underlying diseases, $n$ (%)          |                                      |                           | 0.906     |
| Hypertension                              | 42 (70.00)                           | 40 (66.67)                | 0.882     |
| Diabetes                                  | 33 (55.00)                           | 37 (61.67)                | 0.514     |
| Renal insufficiency                       | 18 (30.00)                           | 14 (23.33)                | 0.492     |
| Arrhythmia                                | 12 (20.00)                           | 9 (15.00)                 | 0.529     |
| Hyperlipidemia                            | 10 (16.67)                           | 14 (23.33)                | 0.364     |
| Hyperuricemia                             | 18 (30.00)                           | 16 (26.67)                | 0.764     |
| Chronic lung conditions                   | 6 (10.00)                            | 4 (6.67)                  | 0.773     |
| Other diseases                            | 4 (6.67)                             | 6 (10.00)                 | 0.772     |
| The reason of heart failure, $n$ (%)      |                                      |                           | 0.839     |
| Ischemic heart disease                    | 41 (68.33)                           | 44 (76.67)                | 0.078     |
| Dilated cardiomyopathy                    | 9 (15.00)                            | 7 (11.67)                 | 0.591     |
| Hypertensive heart disease                | 8 (13.33)                            | 6 (10.00)                 | 0.570     |
| Valvular heart disease                    | 2 (3.33)                             | 3 (1.67)                  | 0.648     |
| Systolic pressure                         | 139.60 ± 10.78                       | 140.82 ± 10.77            | 0.740     |
| Diastolic pressure                        | 83.24 ± 9.38                         | 83.35 ± 9.79              | 0.972     |
| Heart rate, beats per min                 | 86.65 ± 17.97                        | 92.24 ± 14.94             | 0.390     |
| Concentrations of potassium, mmol/L       | 4.32 ± 0.54                          | 4.19 ± 0.58               | 0.472     |
| Creatinine level, μmol/L                  | 103.21 ± 26.0                        | 104.82 ± 26.4             | 0.859     |
| The medication status of ACE inhibitors or ARB before the study, $n$ (%) | 42 (70.00) | 40 (66.67) | 0.695 |
| ACEI                                      | 10 (16.67)                           | 12 (20.00)                | 0.637     |
| enalapril                                 | 6 (10.00)                            | 5 (8.33)                  | 0.752     |
| fosinopril                                | 2 (3.33)                             | 4 (6.67)                  | 0.675     |
| ramipril                                  | 1 (1.67)                             | 2 (3.33)                  | 1.000     |
| perindopril                               | 1 (1.67)                             | 1 (1.67)                  | 1.000     |
| ARB                                       | 32 (53.33)                           | 28 (46.67)                | 0.468     |
| valsartan                                 | 16 (26.67)                           | 13 (21.67)                | 0.522     |
| losartan                                  | 10 (16.67)                           | 8 (13.33)                 | 0.609     |
| telmisartan                               | 4 (6.67)                             | 6 (10.00)                 | 0.509     |
| irbesartan                                | 2 (3.33)                             | 1 (1.67)                  | 1.000     |
| Main medications, $n$ (%)                 |                                      |                           | 0.984     |
| Beta-blockers                             | 54 (90.00)                           | 56 (93.33)                | 0.989     |
| Metoprolol                                | 48 (80.00)                           | 52 (86.67)                | 0.695     |
| Bisoprolol                                | 6 (10.00)                            | 4 (6.67)                  |           |
| Aldosterone antagonists                   | 60 (100.00)                          | 60 (100.00)               | 0.835     |
| Spironolactone                            | 60 (100.00)                          | 60 (100.00)               |           |
| Loop diuretics                            | 60 (100.00)                          | 60 (100.00)               | 0.835     |
| Furosemide                                | 42 (70.00)                           | 47 (78.33)                | 0.297     |
| Torasemide                                | 18 (30.00)                           | 13 (21.67)                |           |
| Digitalis                                 | 48 (80.00)                           | 52 (86.67)                | 0.801     |
| Digoxin                                   | 48 (80.00)                           | 52 (86.67)                |           |
| Antidiabetic                              | 33 (55.00)                           | 37 (61.67)                | 0.720     |
| Hypercholesteremia                        | 10 (16.67)                           | 14 (23.33)                | 0.454     |
| Urate lowering drugs                      | 18 (30.00)                           | 16 (26.67)                | 0.649     |
| Other Drugs                               | 6 (10.00)                            | 4 (6.67)                  | 0.709     |

Before the treatments, there were no statistically significant differences on baseline data of the patients in the two groups, $P > 0.05$.

Detecting the levels of serum hs-cTnT and NT-ProBNP before and after the treatments: As shown in Table III, levels of the serum hs-cTnT and NT-ProBNP in the sacrubitil/valsartan group before the treatments were $(24.47 ± 7.54)$ pg/mL and $(10,356.94 ± 5,447.68)$ pg/mL, respectively; however, levels in the valsartan group were $(29.75 ± 10.03)$ pg/mL and $(9,518.17 ± 5,905.17)$ pg/mL, respectively. There was no statistically significant difference in these levels between the two groups ($P > 0.05$). By con-
The differences between the two groups were statistically significant (P < 0.05). The measurements of LAD, LVEDD, and LVEF in the sacrubutil/valsartan group decreased after the treatments to (17.92 ± 4.74) mm, (64.51 ± 7.12) mm, and (36.47 ± 5.21) %, respectively. The differences between the two groups were statistically significant (P < 0.05). There were also significant differences within the same group, before and after treatment (P < 0.05).

Measuring the value of LAD, LVEDD, and LVEF before and after the treatments: Before the treatment, the measurements of LAD, LVEDD, and LVEF were (49.41 ± 5.22) mm, (68.06 ± 6.20) mm and (31.12 ± 6.65) % in the sacrubutil/valsartan group and (49.65 ± 4.91) mm, (67.06 ± 3.97) mm and (30.41 ± 6.11) % in the valsartan group, respectively. There was no statistically significant difference in these values between the two groups (P > 0.05). The measurements of LAD, LVEDD, and LVEF in the sacrubutil/valsartan group decreased after the treatments to (42.18 ± 4.87) mm, (60.35 ± 7.12) mm, and (45.35 ± 4.49) %, respectively. The differences between the two groups were statistically significant (P < 0.05). There were also significant differences within the same group, before and after treatments (P < 0.05), as shown in Table IV.
Discussion

CHF is a form of clinical syndrome, with dyspnea, edema, and fatigue as its main characteristics. It is caused by persistent myocardial injury leading to a decrease of cardiac pump function, seriously affecting quality of life for patients. Studies showed that the use of a joint test of hs-cTnT and NT-ProBNP exhibits value for clinical diagnosis and prognosis for patients with CHF.16

Hs-cTnT is one of the excitation contraction coupling proteins of cardiomyocytes. Because of its sensitivity, specificity, reproducibility, and lower detection threshold than the traditional cardiac troponin T (cTnT), it has become the gold standard for the diagnosis of myocardial injury19 and is positively associated with the degree of myocardial injury.9 When heart failure occurs, the blood pumping function of the heart declines, causing myocardial ischemia by reducing the perfusion of the coronary arteries; to compensate, heart rate increases rapidly. This eventually leads to injury of the cardiomyocytes, which release of hs-cTnT into blood. More importantly for its role as an assay, the level of hs-cTnT is positively correlated with the severity of the disease,10,11 such that the level of cardiac insufficiency can be gauged and a prognosis determined.12,13

NT-proBNP has been used to diagnose CHF by the ESC since 2005.16 It is a 76 amino acids segment of a N-terminal peptide hormone secreted mainly by ventricular myocardium when stressed, resulting from cleavage of pro-brain natriuretic peptide (proBNP).15,16 NT-ProBNP is more reliable for diagnosing CHF because of its stability, lack of biological activity, good specificity, and sensitivity. It is also not affected by daily activities and postural changes and has a long half-life providing a convenient period for testing. Recent reports showed that the level of serum NT-ProBNP can be used to evaluate cardiac function in patients and provide a prognosis.17,18

A combination of ACE inhibitor, β-blocker, and aldosterone antagonists without contraindications was recommended for patients of heart failure with reduced ejection fraction.20 Even though patients with heart failure are treated with optimized ACEI, β-blocker, and aldosterone antagonists, almost 50% more cases of CHF are predicted by 2030.20 This suggests there is an urgent need to explore new therapeutic drugs and new intervention targets to treat this condition.

Sacrubitril/valsartan is a combination angiotensin receptor blocker-neprilysin inhibitor.21,22 When heart failure occurs, the tension of the left ventricular wall will increase with the increase of cardiac pressure or volume load, and this stresses cardiomyocytes.23 This in turn causes the increased secretion of natriuretic peptide and activation of the renin-angiotensin-aldosterone system (RAAS) through neurohumoral and endothelium regulation. Neprilysin is a key enzyme in the degradation of bioactive natriuretic peptide, which can promote natriuresis and diuresis of vessels. It distributes widely, mainly in the brush border of the proximal renal tubules, but also distributed in cardiomyocytes, smooth muscle cells, and neutrophils, as well as vascular endothelial cells.23 The development of heart failure is also inseparable from the excessive activation of RAAS, which is able to increase inflammatory reactions and results in cardiomyocyte apoptosis and eventually cardiac remodeling.24 In addition, it can increase the level of biologically active natriuretic peptide. Through the inhibitory effect of sacrubitril on neprilysin, reduced degradation of natriuretic peptide and inhibition of RAAS by the ARB valsartan, the combined effect of the two drugs could dilate vessels, promote natriuresis, further inhibit cardiac remodeling, and finally improve the survival rate of patients with heart failure.

In addition to other symptoms, patients with CHF often suffer from chronic cough caused by chronic pulmonary congestion or pneumonedema, which restricts the use of ACEI drugs. It was for this reason that an ARB drug that didn’t cause an irritating dry cough was chosen for the control group.

This study shows that the therapeutic effects of sacrubitril/valsartan, a combination of angiotensin receptor blocker and neprilysin inhibitor, on the clinical treatment of CHF were much greater and the adverse reactions and rehospitalization less than with valsartan alone. We also showed levels of serum hs-cTnT and NT-ProBNP and the measurements of LAD and LVEDD in the two groups far in excess of normal. The LVEF was far below of normal before the treatment. However, after the treatment, the levels of serum hs-cTnT and NT-ProBNP in the two groups declined significantly, the measurements of LAD and LVEDD decreased, and LVEF was improved significantly. This indicated the application of sacrubitril/valsartan, and valsartan as general treatments for patients with CHF could significantly reduce the levels of serum hs-cTnT and NT-ProBNP and significantly improved the measurements of LAD, LVEDD, and LVEF, suggesting that the level of NT-ProBNP decreased may be related to the improvement of heart structure, which also could improve the LVEF. Furthermore, the levels of serum hs-cTnT and NT-ProBNP, the measurements of LAD and LVEDD also significantly declined, and LVEF significantly improved in the same group after the treatments. The improvement of the sacrubitril/valsartan group was more obvious with significant differences, which fully showed that the treatment of CHF with sacrubitril/valsartan was more effective than valsartan.

Limitations: Limitations of this study include the small number of cases enrolled and the relatively short time of observation. The clinical outcome was only evaluated through adhoc-defined categories of improvement and also with risk of spurious findings. We chose the patients aged >60 year, and NYHA Class II-IV may result in bias of selection eventually influencing data. In addition, patients with heart failure also often exhibit other associated diseases, and drug interactions from the treatment of these conditions may affect the clinical outcomes pertinent to this study. More importantly, clinical use of sacrubitril/valsartan, an expensive drug, might have been limited by family economic factors, which mainly affect the clinical use. This situation might be improved by increasing government investment or decreasing the price of sacrubitril/valsartan. We see this study as the start of an ongoing effort to monitor our experience with these drugs in China.
Conclusions

Sacubitril/valsartan treatment of patients with CHF improves their symptoms and is deserving of clinical application. This is also evident from significantly improved levels of serum hs-cTnT and NT-ProBNP and the left ventricular function.

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Disclosure

Conflicts of interest: The authors have no conflicts of interest to declare.

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