Effect of Sacubitril/Valsartan on VEGF, VEGFR-1 and Left Ventricular Remodeling in Patients with Heart Failure with Decreased Ejection Fraction

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ABSTRACT

Background: Sacubitril/valsartan has been shown to reduce mortality and reduce hospitalization in patients with heart failure with reduced ejection fraction (HFREF), but it has not been reported for endothelial function and left ventricular remodeling in patients with heart failure. Endothelial cell dysfunction is involved in the progression of heart failure.

Hypothesis: So, we hypothesized that Sacubitril/valsartan improves left ventricular remodeling and prognosis in patients with heart failure by affecting VEGF and VEGFR-1.

Methods: From October 2018 to May 2019, 63 patients with heart failure who had been hospitalized in the Department of Cardiology of Jinan People’s Hospital were selected. According to the treatment plan, they were divided into control group (37 cases) and observation group (26 cases). Patients in the control group underwent routine anti-heart failure treatment. Patients in the observation group were replaced with angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor antagonist (ARB) in the conventional anti-heart failure treatment regimen. Valsartan; both groups of patients were treated for 3 months. The levels of NT-proBNP, VEGF, VEGFR-1 and cardiac structural parameters were compared before and after treatment in the two groups.

Results: There were significant differences in VEGF, VEGFR-1 and pro-BNP between the two groups after treatment.

Conclusion: After 3 months of treatment with Sacubitril/valsartan, patients with heart failure with reduced ejection fraction improved left ventricular systolic function, increased plasma VEGF levels, and decreased NT-proBNP and VEGF-1R levels.

Introduction

Percutaneous Coronary Intervention (PCI) completely altered the management and treatment of acute Myocardial Infarction (MI) [1,2]. It is a reperfusion strategy for the entire developed country, with only 90,000 operations performed annually in the United States [3,4]. The introduction of PCI and adjuvant therapy have reduced hospital mortality after acute Myocardial Infarction from 20% in the late 1980s to about 5%-7% in the modern series [5,6]. Heart failure after Myocardial Infarction remains a major driver of coronary heart disease in patients with advanced morbidity, mortality, and medical costs. There is therefore an urgent need to explore new therapies for patients with reduced ejection fraction.

A new type of drug for the treatment of heart failure, Sacubitril/valsartan, has been developed, a salt complex crystal composed of...
receptor antagonist (ARB), spironolactone treatment, etc., and adjust the treatment according to the primary disease; patients in the observation group replaced the ACEI/ARB in the conventional anti-heart failure treatment plan with Sacubitril/valsartan (Beijing) Novartis Pharmaceutical Co., Ltd. produces, Chinese medicine quasi-word H20170344), starting dose 25 mg / time, 2 times / d, then gradually increase the dose, the maximum dose is 400 mg / d, in order to overlap the risk of angioedema caused by ACEI To the lowest, before the start of the use of Using an open-ended test, the observation group and the control group were randomly divided according to the random number table method.

Patients in the control group were treated with conventional anti-heart failure, including rest, salt restriction and diuretics, digitalis preparations, vasodilators, beta-blockers, Angiotensin-Converting Enzyme Inhibitors (ACEI)/Angiotensin Receptor II Receptor Antagonist (ARB), spironolactone treatment, etc., and adjust the treatment according to the primary disease; patients in the observation group replaced the ACEI/ARB in the conventional anti-heart failure treatment plan with Sacubitril/valsartan (Beijing) Novartis Pharmaceutical Co., Ltd. produces, Chinese medicine quasi-word H20170344), starting dose 25 mg / time, 2 times / d, then gradually increase the dose, the maximum dose is 400 mg / d, in order to overlap the risk of angioedema caused by ACEI To the lowest, before the start of the use of Sacubitril/valsartan ACEI should be given at least 36 h for drug elution, the rest of the treatment with the control group. Both groups of patients were treated continuously for 3 months.

Combination therapy with ACE inhibitor (or ARB) and Sacubitril/valsartan is strictly prohibited. Two groups of patients underwent routine clinical examination before treatment with anti-heart failure, 12-lead electrocardiogram (ECG), transthoracic echocardiography (TTE) and Doppler assessment. The same measurement was repeated at 3 months. Cardiac function assessment was performed using NYHA classification. / valsartan, ACEI should be given at least 36 h for drug elution, the rest of the treatment with the control group. Both groups of patients were treated continuously for 3 months. Combination therapy with ACE inhibitor (or ARB) and Sacubitril/valsartan is strictly prohibited. Two groups of patients underwent routine clinical examination before treatment with anti-heart failure, 12-lead electrocardiogram (ECG), transthoracic echocardiography (TTE) and Doppler assessment. The same measurement was repeated at 3 months. Cardiac function assessment was performed using NYHA classification. and valsartan (LCZ696) in a 1:1 molar ratio [7], PARADIGM-HF [ARNI vs. ACEI (a prospective comparison of angiotensin-converting enzyme inhibition to determine the overall mortality and morbidity of heart failure) study] is a phase III, randomized, double-blind trial evaluation. The safety and efficacy [8] of LCZ 696 and enalapril in patients with chronic symptomatic HFrEF can reduce all-cause mortality in patients with chronic HFREF by 16%, cardiovascular mortality by 20%, and HF hospitalization by 21%. However, in this landmark trial, the serum markers VEGF, VEGFR-1 and endothelial cell-controlled signaling pathways that do not clearly determine. Endothelial cell-controlled signaling pathways play a crucial homeostatic role in cardiac tissue and disorders of these pathways can lead to poor myocardial remodeling and dysfunction in heart failure, suggesting a poor prognosis in these patients.

Vascular Endothelial Growth Factor (VEGF) is a platelet-derived growth factor supergene family secreted by Endothelial Cells and plays a central role in regulating angiogenesis and lymphangiogenesis. VEGF-A is a major angiogenic factor that binds to two Tyrosine Kinase (TK) receptors, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flik-1), and regulates proliferation of endothelial cells, migration, vascular permeability, secretion and other small molecule proteins or peptides. Our study aimed to evaluate the effect of Sacubitril/valsartan on endothelial cell function (VEGF/ VEGFR-1) and to further provide new therapeutic targets and clinical markers for heart failure.

Methods

The study was approved by our Institutional Committee on Human Research. No extramural funding was employed to support this work. The authors are solely responsible for study design and conduct, study analyses, drafting and editing of the paper, as well as its final editorial content.

Patient Selection

From June 2017 to September 2018, patients with heart failure who had a reduced ejection fraction in the Department of Cardiology of Jinan City People's Hospital.

Standard Constrain: The patient is at least 18 years of age, with New York Heart Association (NYHA) II, III or IV symptoms and an ejection fraction of no more than 40%. The patient was asked to be hospitalized for heart failure in the past 12 months. Consider patients who do not take any ACE inhibitors or ARB, or who take a steady dose of beta blockers, ACE inhibitors or ARB for at least 4 weeks.

Exclusion Criteria: Including symptomatic hypotension, systolic blood pressure <100 mmHg, estimated glomerular filtration rate (eGFR) below body surface area 30 mL / min / 1.73 m2, serum potassium level > 5.2 mmol / L during screening, history of angioedema Or unacceptable side effects occur with ACE inhibitors or ARB treatment. Other exclusion criteria were as follows: correctable valvular disease; <3 months of acute coronary syndrome; recent coronary revascularization within the last 3 months, or planned revascularization. According to previous studies, an (absolute) improvement in LVEF ≥ 5% is considered to be an important response to shakuba/valsartan [9, 10].

Study Procedures

Using an open-ended test, the observation group and the control group were randomly divided according to the random
number table method. Patients in the control group were treated with conventional anti-heart failure, including rest, salt restriction and diuretics, digitalis preparations, vasodilators, beta-blockers, Angiotensin-Converting Enzyme Inhibitors (ACEI)/Angiotensin Receptor II Receptor Antagonist (ARB), spironolactone treatment, etc., and adjust the treatment according to the primary disease; patients in the observation group replaced the ACEI/ARB in the conventional anti-heart failure treatment plan with Shakuba / valsartan (Beijing Novartis Pharmaceutical Co., Ltd. produces, Chinese medicine quasi-word H20170344), starting dose 25 mg / time, 2 times / d, then gradually increase the dose, the maximum dose is 400 mg / d, in order to overlap the risk of angioedema caused by ACEI To the lowest, before the start of the use of Sacubitril/valsartan, ACEI should be given at least 36 h for drug elution, the rest of the treatment with the control group. Both groups of patients were treated continuously for 3 months. Combination therapy with ACE inhibitor (or ARB) and Sacubitril/valsartan/valsartan is strictly prohibited. Two groups of patients underwent routine clinical examination before treatment with anti-heart failure, 12-lead electrocardiogram (ECG), transthoracic echocardiography (TTE) and Doppler assessment. The same measurement was repeated at 3 months. Cardiac function assessment was performed using NYHA classification.

Echocardiographic Measurements

Vivid E9, GE Healthcare, (USA) was used to detect patients taking the left lateral position and synchronizing the ECG. Subjects underwent routine cardiac ultrasound by an experienced cardiac sonographer (without knowing the patient’s condition), using an s3 ultrasound probe with a probe frequency of 2.5 MHz and measuring left ventricular structural parameters such as end-systolic and diastolic at a standard plane recommended by the American Society of Ultrasound. End diameter (LVIDs, LVIDd), posterior wall end-systolic and end-diastolic thickness (LVPwTs, LVPWTd), systolic and end-diastolic volume (LVESV, LVEDV), systolic function (LVEF), diastolic function (E/A, EDT, IVRT) Routine indicators, left and right ventricle and left and right ventricle (LA, LV) in the apical four-chamber view. All indicators were measured continuously for 3 cycles. All echocardiograms are read, reviewed, and diagnosed by trained experts. LVEF: Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) were measured using the Simpson method. LVEF = (LVEDV - LVESV) / LVEDV × 100%.

Detection of VEGF and VEGFR-1

The kit uses a double antibody one-step sandwich enzyme-linked immunosorbent assay (ELISA). The coated microcapsules, which are pre-coated with Vascular Endothelial Growth Factor (VEGF) antibody and Vascular Endothelial Growth Factor receptor 1 (VEGFR-1) antibody, are sequentially added with specimens, standards, and HRP-labeled detection antibodies. Breed and wash thoroughly. Using the substrate TMB to develop color, TMB is converted to blue under the catalysis of peroxidase and converted to the final yellow color by the action of an acid. The color depth is positively correlated with VEGF and VEGFR-1 in the sample. The absorbance (OD value) was measured at 450 nm using a microplate reader to calculate the sample concentration.

Statistical Analysis

Data analysis was performed using SPSS 13.0 statistical software. The measurement data were expressed as mean ± SD. The t test was used for comparison between groups. The paired t test was used for comparison within the group. The χ2 test was used for the analysis of the count data test. The difference was statistically significant at P < 0.05. The skewed distribution data is converted to a normal distribution (represented by the median) by log logarithm.

Results

Population

All patients were divided into control group (37 cases) and observation group (26 cases) according to the treatment plan. There were no significant differences in age, height, body weight, HR, BSA, Cr and NT-proBNP between the two groups (P>0.05, Table 1). There were no significant differences in left ventricular structural parameters (LVEF), VEGF and VEGFR-1 between the control group and the observation group (P>0.05). (See Tables 1 & 2).

Comparison of Indicators Between the two Groups after Treatment

Comparison between the two groups after treatment: Compared with before treatment, the cardiac structural parameters (AO, LVIDs, LA) and lgNT-proBNP in the control group were larger than those in the observation group, and the systolic function index (LVEF) was lower than that in the observation group. The difference was statistically significant (P<0.05). The VEGF of the control group was significantly lower than that of the observation group, and the level of VEGF-1R was higher than that of the observation group, and the difference was statistically significant (P<0.05) (See Table 3).

Comparison of Indicators in the two Groups after Treatment

Comparison between the two groups after treatment: Compared with before treatment, the cardiac structure index and lgNT-proBNP were significantly decreased in the observation group, and the systolic function index was significantly increased, the difference was statistically significant (P<0.05), before treatment. There was no significant difference in RA between the observation group and the control group (P>0.05). There were statistical changes between the control group and other indicators except PWTs, RA, RV, VEGF and VEGF-1R. Academic significance (P<0.05) (See Table 4).

Correlation Analysis between VEGF and lgNT-proBNP, VEGF-1 and lgNTproBNP

The results showed that VEGF and lgNT-proBNP were positively correlated after treatment, with a coefficient of 0.534 (P<0.05) (Figure 1). VEGF-1 and lgNT-proBNP were also positively correlated after treatment, with a coefficient of 0.459. (P<0.05) (Figure 2).
Discussion

Heart failure is defined as "a clinical syndrome caused by any structural or functional heart disease that impairs ventricular congestion or discharge of blood" [11]. This has been translated into several validated diagnostic criteria (eg, the Framingham standard [12] and the European Society of Cardiology standards [13]). Early studies of heart failure after Myocardial Infarction used clinical criteria such as the classification criteria of Killip and the New York Heart Association [14,15]. Although succinct, the Killip grading retains prognostic value in recent cohort studies (eg, the GRACE registry): hospitalization mortality in patients with Killip class I is 3%, and in patients with class III is 20% [16]. In patients with PCI, a higher Killip grading is an independent predictor of hospitalization and 6-month mortality [17]. The development of echocardiography has improved the clinical HF score, which led to an objective measurement of ejection fraction and ventricular volume, which is an intrinsic part of HF diagnosis [18].

There are several overlapping mechanisms of HF after myocardial infarction. Early onset of HF in acute Myocardial Infarction is due to myocardial shock, myocardial necrosis, previous HF decompensation or a combination of acute mitral regurgitation due to papillary muscle dysfunction. Heart failure during hospitalization may also be due to any of the above reasons, accompanied by fluid or contrast overload, renal insufficiency or complications such as ventricular septal defect or cardiac tamponade. Late stages of heart failure reflect the consequences of simultaneous myocardial cell death and scar formation and ventricular remodeling. In the 1960s, Killip first used heart failure after Myocardial Infarction as a prognostic feature of poor prognosis. Heart failure is associated with extensive Myocardial Infarction and multivessel disease, and impaired ventricular function leads to increased mortality [19]. Therefore, the treatment of heart failure after Myocardial Infarction remains a major challenge.

Sacubitril/valsartan is the first renin-angiotensin-aldosterone system (RAAS) and enkephalinase double blocker, and its complementary mechanisms overlap. It is currently the "breakthrough" drug for the treatment of heart failure. The 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [20] is the first recommendation to use Sacubitril/valsartan for heart failure. Enkephalinase [8] is a membrane-bound endopeptidase that hydrolyzes the atria, brain and C-type natriuretic peptides and other endogenous vasodilators, such as adrenomedullin and bradykinin, to clear the above peptides. The main enzyme of the class. Thus, inhibition of enkephalinase leads to elevated levels of natriuretic peptides, with several potential benefits such as diuretic effects and vasodilation [7], dual inhibition of RAAS and enkephalinase translates into angiotensin II-mediated hypertrophy or fibrosis, as well as beneficial anti-proliferative and anti-hypertrophic effects. In general, natriuretic peptides are secreted by excessive blood volume and increased left ventricular filling pressure, which is a common feature in patients with heart failure. Therefore, Shakuba Qusarsartan helps regulate sodium and water balance, blood volume, arterial blood pressure and sympathetic inhibition. The PARADIGM HF study demonstrates the striking clinical benefits of LCZ696, primarily because of a significant reduction in the primary composite endpoint of cardiovascular death or HF hospitalization, and a reduced risk of death for any reason. Although the clinical benefits of shakuba/valsartan have been well documented to support the expected potential physiological mechanisms, other effects on tissue remodeling have not been well documented [21].

The mammalian genome encodes five VEGF family members, VEGF-A (also known as VEGF), placental growth factor (PlGF), VEGF-B, VEGF-C and VEGF-D, which regulate angiogenesis, angiogenesis and lymphangiogenesis [22, 23].

In particular, VEGF-A is critical for angiogenesis during early embryogenesis. Due to the formation of immature blood vessels, not only VEGF-A homozygous knockout mice but also heterozygous mice (VEGF-A +/-) showed an embryonic lethal phenotype, indicating that VEGF-A in embryos must be strictly controlled [24, 25]. Several VEGF-A subtypes were generated by alternative splic-
ing. Among them, VEGF-A165 has the highest biological activity and has binding affinity to the co-receptor Neuropilin-1 (Nrp1). Recently, another spliced form of VEGF-A, VEGFxxxb, has been reported. VEGFxxxb has a lower affinity for the receptor and competes with VEGF-A, thereby negatively regulating angiogenesis [26].

In 1990, researchers isolated a gene encoding a novel Tyrosine Kinase (TK) receptor from human placenta. The TK receptor has seven immunoglobulin (Ig)-like domains in the extracellular region, while the TK domain has a 60 amino acid long kinase insert [27]. Based on structural similarity, we named it Fms-like TK-1 (Flt-1). In 1992, Flt-1 was shown to bind to VEGF/vascular permeability factor and is now known as VEGFR-1 [28]. Unlike VEGFR-2, VEGFR-1 has a high affinity for its ligand VEGF, and its affinity is about an order of magnitude higher than that of VEGFR-2 [29]. However, the kinase activity of VEGFR-1 is low, about one tenth of that of VEGFR-2. The VEGFR-1 gene produces two major proteins: the full-length receptor and sFlt-1 [30]. These facts suggest that VEGFR-1 may have a negative regulatory effect on angiogenesis in some cases. The study found that VEGFR-1 negatively regulates angiogenesis during early embryogenesis by capturing VEGF and decreasing the pro-angiogenic signal of VEGF-2 [31].

The study found that LCZ696 acts in parallel with the NO-sGC-cGMP pathway by activating the NP-pCG-cGMP signaling system, which increases diuresis and vasodilation. They also enhance myocardial relaxation through signaling pathways that are dependent on cardiac endothelial cells. Increasing cGMP production to reduce cardiac hypertrophy [32], inhibition of angiotensin receptors leading to inhibition of the renin-angiotensin-aldosterone system, which has been shown to be beneficial in heart failure, is consistent with our findings. Shakuba Qusarsartan improved left ventricular remodeling. The heart is a muscle pump composed of cardiomyocytes, Endothelial Cells (EC), fibroblasts, stem cells and inflammatory cells [33]. Cardiac tissue is a highly organized structure of cells and extracellular matrices with complex multi-directional communication between cells. All cells present in the myocardium secrete autocrine, juxtaposition and paracrine factors that regulate the function of neighboring cells. Intercellular communication plays a crucial role in the development of heart and normal heart function in adult organisms, and plays a crucial role in the pathophysiology of cardiac remodeling and heart failure development. In particular, factors secreted by cardiac microvascular EC play a crucial role in normal cardiac function and cardiac remodeling. During the pathophysiological development of heart failure, changes in hemodynamic and mechanical factors, as well as hypoxia, stimulate cardiomyocytes to release angiogenic growth factors, thereby inducing parallel growth of the supply vessels.

Vice versa, activated or dysfunctional Endothelial Cells may also affect the function of other types of cells in the heart. The study found that the pro-angiogenic effect of β-adrenergic receptor blockade in rat hearts was reduced by the administration of bait Vascular Endothelial Growth Factor (VEGF) receptor (Ad-Flk) [34]. The positive nutrient effect of endothelial cell-derived nitric oxide (NO) leads to earlier relaxation episodes and longer diastolic phase [35] may also play a role in stimulating cardiac angiogenesis. Therefore, we found that the VEGF level in the observation group was significantly higher than that in the control group. Therefore, it is speculated that LCZ696 activates the NP-pCG-cGMP signaling system, activates Endothelial Cells to produce VEGF, stimulates angiogenesis and improves cardiomyocyte hypertrophy, and can pass endothelial cells. The paracrine function and intercellular signal series delay the fibrosis of cardiomyocytes; while the improvement of myocardial blood flow and left ventricular function directly stimulates the endothelial erbB receptor through autocrine, indirectly by increasing the expression of VEGF and angiopoietin-1 [36].

Cardiac Endothelial Cells not only respond to hemodynamic forces and paracrine signals of adjacent cells, but also actively participate in the cardiac remodeling process by stimulating the growth and contraction of cardiomyocytes or the production of extracellular matrix proteins in myoblasts. Furthermore, in response to appropriate signals, they may alter their phenotype and differentiate into extracellular matrix producing cells. Since cardiac angiogenesis plays a central role in the transition from adaptive cardiac hypertrophy to heart failure, Endothelial Cells and signaling mechanisms involved in the regulation or regulation of cardiac angiogenesis represent the potential to improve cardiac remodeling and prevent stress overload. A therapeutic target for arrhythmias.

Author Contributions

Han Xia designed this research. Wu Menghai analyzed the data, Han Xia wrote the paper. Wu Menghai and Li Liu carried out experiments. Wu Menghai analyzed the data, Han Xia wrote the paper.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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