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Comparison of valsartan and benazepril when combined with atorvastatin in protecting patients with early cardio-renal syndrome (CRS)

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Abstract. – OBJECTIVE: The aims to investigate the different protective effects of valsartan and benazepril when combined with atorvastatin in the cardio-renal functions of cardio-renal syndrome (CRS) patients.

PATIENTS AND METHODS: A total of 200 early CRS patients were enrolled in the present study, including 104 males and 96 females, with an average age of 62.2 ± 7.7 years. The same group of patients were set as the control group prior to treatment, and then randomly divided into two groups; the A group was treated with valsartan (80 mg/d) and atorvastatin (20 mg/d); the B group was treated with benazepril (10 mg/d) and atorvastatin (20 mg/d). The treatment period was 24 months.

RESULTS: The clinical efficacy and clinical events were observed and the following parameters of each patient were measured before and after treatment: 24h urine protein; creatinine clearance; serum brain natriuretic peptide (BNP); high sensitivity C-reactive protein (hsCRP); blood lipid level; liver function and ejection fraction (EF) value. Compared with the control group, the clinical symptoms of the treatment groups were improved with decreased blood lipid levels, significantly decreased serum BNP and hsCRP levels and significantly increased EF values and creatinine clearance rates ($p < 0.01$). The differences between the two treatment groups were not statistically significant. The number of patients that stopped treatment due to the development of a cough was significantly higher in the B group than the A group ($p < 0.01$).

CONCLUSIONS: When combined with atorvastatin, both valsartan and benazepril effectively improved the cardio-renal functions of early CRS patients. There was no significant difference between the two treatments however, valsartan appeared to be better tolerated by patients.

Key Words:
Valsartan, Benazepril, Atorvastatin, Cardio-renal syndrome.

Introduction

The broad definition of cardio-renal syndrome (CRS) refers to cardio-renal functional disorders caused by acute (or chronic) cardiac or renal dysfunction through a series of neurohormonal feedback mechanisms. This syndrome emphasizes the close ties between these two organs and can be divided into five types, among which the chronic CRS would be much more is often easily to be overlooked[1,2]. With Chinese economic development, the aged population has gradually increased, and concurrently, the number of chronic CRS patients has also gradually increased. The majority of these patients presented with significantly impaired heart and kidney functions and, therefore, the prognosis was extremely poor. Currently, there is no effective treatment program for chronic CRS; with the emphasis primarily being on early diagnosis and early treatment. Previous studies have suggested that the pathophysiological mechanisms of CRS might include: hemodynamic changes, endothelial dysfunction, inflammation, and activation of the renin-angiotensin-aldosterone system (RAAS) and/or the sympathetic system. Any change in these risk factors could cause a cascade of other factors, thus lead to a vicious cycle, and cause damages of cardio-renal structures and functions seen in this syndrome[3,4]. The subcutaneous injection of isoproterenol and three-fourth kidney resection to form the chronic CRS animal model[5], and confirmed the existence of its pathological mechanisms of CRS. In addition, numerous studies have confirmed that angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) had a protective effect in the patients with heart failure and renal dysfunction[6]. Furthermore, that statins could not only regulate the

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lipid, but also have more pleiotropic effects, and may play a protective role in chronic heart failure and renal dysfunction[7,8]. In a previous study[9] conducted in the authors' laboratory, combined with statins, Valsartan and benazepril improved the cardio-renal functions of CRS rats, with no difference between the two medications. Consequently it was hypothesized that regardless of activation of ACEI or ARBs, the combination of these peptides with statins can play a stronger cardio-renal protective role. In addition to the synergetic effects towards AT1-R, this mechanism might be associated with the simultaneous cardio-renal protective effects that delay the progress of CRS. There is currently no report about whether valsartan and benazepril would have similar effects in the early chronic CRS patients when combined with atorvastatin. The current study observed the different of cardio-renal protective effects of ARB and ACEI in the early CRS patients when combined with statins, aiming to provide insights and evidence of evidence-based medicine for early intervention in CRS patients.

Patients and Methods

Study Subjects

Patients with early chronic heart failure associated with renal dysfunction, who were firstly admitted into the Department of Vasculocardiology, Puai Hospital, Wuhan, China, from June 2011 to June 2012 while that were untreated or did not take ARB and ACEI, were enrolled in the current study. The inclusion criteria include a diagnosis of early chronic heart failure according to the Framingham criteria, cardiac functions were classified as grade II-IV according to the NYHA standard; echocardiographic of left ventricular ejection fraction (EF) of 40% < EF < 50%; relatively stable conditions (hemodynamically stable, without the need of vasoactive drugs for maintenance), early chronic renal failure criteria of: 50 ml/min < Ccr (creatinine clearance rate) < 80 ml/min. The exclusion criteria: patients with: Cr > 265 umol/minl; systolic pressure ≤ 90 mmHg; acute coronary syndrome; various malignancies; chronic obstructive lung disease; allergy to statins allergy; severe hepatic insufficiency with, primary renal diseases and; severe exercise-induced proteinuria. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Huazhong University of Science & Technology. Written informed consent was obtained from all participants.

General Patient Information

A total of 200 CRS patients were enrolled in the current study, and were randomly divided into the Valsartan group and the benazepril group (n = 100 cases each group), the indicators and ratios of patients using β-receptor blockers and aldosterone, as well as t general clinical information ($p > 0.05$, Table I).

Treatment Methods

Currently, heart failure guidelines clearly propose that ACEI or ARB be the basic treatment. Due to the ethical reason, all patients were set as the control group before the treatment, without the placebo. The patients were then divided into the two treatment groups; control group, the A group was treated with valsartan (80 mg/d) and atorvastatin (20 mg/d); the B group was treated with benazepril (10 mg/d) and atorvastatin (20 mg/d). Both groups were treated with other medications according to their disease conditions, except for any additional kidney-protective drugs. Atorvastatin was produced by Pfizer (Berlin, Germany), valsartan and benazepril were produced by Novartis (St. Louis, MO, USA). The treatment was continued for 24 months, and was stopped in patients that appeared with more than 3-fold increased liver

Table I. Concentrations of Scr, BUN, BNP, ALD, Ang II, CRP and urine protein.

Group	Scr (umol/l)	BUN (mmol/l)	BNP (pg/ml)	ALD (pg/ml)	Ang II (pg/ml)	CRP (μg/l)	Urine-protein (mg/24h)
Control	77.5 ± 8.7	10.2 ± 1.5	56.5 ± 4.6	137.6 ± 16.1	816.3 ± 57.2	568.5 ± 42.1	70.5 ± 12.7
Ato	75.8 ± 8.5$^{\Delta}$	10.0 ± 1.6$^{\Delta}$	56.1 ± 4.3$^{\Delta}$	135.3 ± 16.5$^{\Delta}$	823.2 ± 76.1$^{\Delta}$	580.5 ± 43.2$^{\Delta}$	72.6 ±12.5$^{\Delta}$
Ben+Ato	75.3 ± 8.9$^{\Delta}$	10.4 ± 1.6$^{\Delta}$	56.0 ± 4.8$^{\Delta}$	136.3 ± 15.5$^{\Delta}$	827.8 ± 73.4$^{\Delta}$	576.5 ± 45.2$^{\Delta}$	72.0 ± 13.5$^{\Delta}$
Val+Ato	77.8 ± 9.3$^{\Delta}$	10.3 ± 1.8$^{\Delta,*}$	57.0 ± 5.3$^{\Delta}$	134.6 ± 13.8$^{\Delta}$	835.3 ± 68.9$^{\Delta}$	565.3 ± 45.6$^{\Delta}$	72.0 ± 15.3$^{\Delta}$

Note: Compared with Control group, $^{\Delta}p > 0.05$.

enzymes or drug allergic reactions, too much increased CCr during the treatment period (increased by > 30%), or other non-tolerated adverse reactions, as well as major clinical cardiovascular events (ACS, worsened heart failure requiring hospitalization and or cardiac death) and non-cardiovascular events (cerebrovascular events and non-cardiac death).

Laboratory Testing

Serum blood urea nitrogen (BUN), Cr, blood lipid and liver function were detected by the automatic biochemical analyzer Creatinine clearance was calculated as Ccr = K × [(140-age) × body weight (kg)] / Scr (umol/L)], K = 1.23 (male) or 1.04 (female). The 24h urine protein, serum BNP and hsCRP were detected and the cardiac Doppler ultrasound performed to examine EF. The hepatonephric functions were rechecked every three months.

Clinical Observation and Efficacy Determination

The clinical signs and symptoms included oppression in chest, difficult breathing, palpitations, heart rate, blood pressure and pulmonary rale. At the same time, the 6-min walking distance was tested before and after the testing. Significantly effective (SE): the symptoms of heart failure disappeared after the treatment or the heart functions were improved by grade II or the 6-min walking distance was increased by 2 levels; effective: the symptoms of heart failure were significantly improved, the heart functions were improved by grade I, and the 6-min walking distance was improved by 1 level; ineffective: symptoms of heart failure was not improved or even deteriorated, the cardiac functions and 6-min walking distance wasn't increased. Total efficiency was equal to (SE + effective) / total patients.

Statistical Analysis

The SS15.0 statistical software was used. Measurement data were expressed as $\bar{x} \pm s$, χ^2 test was used to comparison of intergroup composition, and t test was used to comparison of intergroup independent sample. $p < 0.05$ was considered statistically significant.

Results

General Patients Information

During 24-month follow-up, most patients achieved the remission of clinical symptoms. The treatment was effective, while several patients appeared a variety of complicated clinical symptoms, with 89 and 80 cases in the A and B group, respectively, the specific reasons were showed in Table II. The intergroup comparison revealed that except for the patients in the B group who quit the treatment because they could not tolerate the cough were significantly increased ($p < 0.05$), there was no intergroup difference among other events ($p > 0.05$).

Comparison of Liver Functions and Blood Lipid Levels Among the Three Groups

After 48-week treatment, compared with the control group, the blood lipid levels of the treatment groups were significantly decreased, and the difference was statistically significance ($p < 0.01$), and the difference between the two treatment groups showed no statistically significance. There was no significant difference in the liver functions before and after the treatment among the patients ($p > 0.05$) (Table III).

Comparison of Blood Pressure, EF Values and 6-min Walking Distance Between the Treatment Groups

The patients who completed the follow-up, compared with the control group, the blood pres-

Table II. Concentrations of Scr, BUN, BNP, ALD, Ang II, CRP and urine protein 4 weeks after the treatment.

Group	Cr (umol/l)	BUN (mmol/l)	BNP (pg/ml)	ALD (pg/ml)	Ang II (pg/ml)	CRP (μg/l)	Urine-protein (mg/24h)
Control	89.8 ± 9.5	12.2 ± 2.5	89.5 ± 6.9	230.5 ± 30.5	1023.2 ± 86.4	702.8 ± 63.2	102.5 ± 16.3
Ato	75.6 ± 9.3**	10.0 ±2.3	71.6 ± 9.6***	180.3 ± 50.8*	1005.8 ± 108.3	546.3 ± 40.9***	80.6 ± 15.6**
Ben+Ato	63.8 ± 8.6$^{***,\#}$	7.2 ± 2.9$^{***,\#}$	48.9 ± 10.2$^{***,\#\#\#}$	145.8 ± 42.3***	838.3 ± 205.2$^{*,\#}$	450.9 ± 38.5$^{***,\#\#\#}$	64.6 ± 13.4$^{***,\#}$
Val+Ato	60.6 ± 9.8$^{***,\#\#,\Delta}$	7.6 ± 2.0$^{***,\#,\Delta}$	46.5 ± 6.5$^{***,\#\#\#,\Delta}$	140.7 ± 45.2$^{***,\#,\Delta}$	1106 ± 102.9	460.9 ± 36.5$^{***,\#\#\#,\Delta}$	62.1 ± 10.3$^{***,\#\#,\Delta}$

Note: Compared with control group, $^{*}p < 0.05$, $^{***}p < 0.001$; compared with Ato group, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$; compared with Ben+Ato group, $^{\Delta}p > 0.05$.

Table III. Comparison of left ventricular function and hemodynamic parameters among four groups.

Group	LVSP (mmHg)	LVDP (mm Hg)	LVEDP (mm Hg)	dp/dtmax (mmHg/s)	dp/dtmax (mm Hg/s)
Control	96.5 ± 10.2	4.2 ± 1.9	8.6 ± 2.2	4358 ± 732	-3500 ± 870
Ato	110.6 ± 13.6*	2.3 ± 1.8*	5.6 ± 2.0*	5500 ± 965*	-4500 ± 968*
Ben+Ato	128.8 ± 12.3***.###	1.2 ± 1.6***	2.3 ± 2.2***.###	6500 ± 865***.#	-5320 ± 785***
Val+Ato	130 ± 18.9***.###,Δ	1.3 ± 1.2***Δ	2.8 ± 1.6***.###.Δ	6598 ± 436***.###,Δ	-5600 ± 830***.##,Δ

Note: Compared with control group, $*p < 0.05$, $***p < 0.001$; compared with Ato group, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$; compared with Ben+Ato group, $^{\Delta}p > 0.05$.

sure was decreased, the EF value and 6-min walking distance were increased, and the difference was statistically significance ($p < 0.001$), but the difference between two treatment groups was not statistically significance ($p > 0.05$, Table IV).

Comparison of Renal Function, Serum BNP and hsCRP Among the Three Groups

Compared with the control group, the renal functions of the treatment groups were significantly improved, the creatinine clearance rate was increased, and the 24h urine protein was decreased significantly, accompanied with the significant decreasing of serum BNP and hsCRP ($p < 0.001$), while the difference between the two treatment groups was not statistically significance ($p > 0.05$, Table V).

Discussion

Currently, there was no uniform guideline in the chronic CRS patients' treatment. Various chronic heart failure guidelines all recommend ACEI as the treatment cornerstone, and ARB as the alternative medicine for the ACEI intolerance. With the accumulation of ELITEII, OPTIMAAL and VALIANT researches, currently, the role of the ARB drugs in the treatment of heart failure has been much more clear[10,11]. JIKEI HEART test indicated that the Asian populations may benefit more from valsartan-based treatment programs[11]. However, neither ACEI nor ARB can completely inhibit (RAS) activation individually. Aside from RAS activation, CRS progress also involves inflammation and oxidative stress. Therefore, the addition of a full blocking RAS system, endothelial function improvement and oxidative stress and vascular inflammatory reaction reduction are necessary for further improving prognosis. If the RAS system is blocked, the endothelial function is improved and oxidative stress and vascular inflammation are reduced, the prognosis can be improved. In addition to the lipid-regulation effects, statins also had such pleiotropia as anti-inflammatory, antioxidant, endothelial function protection, nerve humoral factor regulation, and could reduce or delay the onset and progression of chronic heart failure[12]. Certain clinical studies did not support the above views[13]. The clinical observation of statins combine with ACEI or ARB in treating the patients with heart failure showed that the ventricular remodeling could be further improved and such inflammatory cytokines as CRP could be further declined, the combination of statins and ARB drugs effective in synergistic vascular protective. However, it lacked large-scale clinical observation and comparative study. More and more evidence showed that the patients with early renal

Table IV. Comparison of LVW/BW among four groups.

Group	LVW (g)	BW (kg)	LVW/BW (g/kg)
Control	0.68 ± 0.06	0.26 ± 0.04	2.81 ± 0.15
Ato	0.61 ± 0.03	0.30 ± 0.03	2.48 ± 0.32**
Ben+Ato	0.50 ± 0.04	0.34 ± 0.03	1.50 ± 0.33***.###
Val+Ato	0.49 ± 0.05	0.33 ± 0.02	1.59 ± 0.26***.###.Δ

Note: Compared with control group, $*p < 0.05$, $***p < 0.001$; compared with Ato group, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$; compared with Ben+Ato group, $^{\Delta}p > 0.05$.

Table V. Comparison of renal function, serum BNP and hsCRP among the three groups.

Group (cases)	Ccr ml/min	Ur-pro mg/24h	BNP pg/ml	hsCRP
Control group (200)	61.4 ± 6.4	440.8 ± 250.0	746.9 ± 341.8	10.2 ± 2.9
A group (89)	65.8 ± 8.4*	296.2 ± 187.1*	452.1 ± 223.6*	7.7 ± 2.7*
B group (80)	65.4 ± 8.4*,Δ	312.9 ± 197.9*,Δ	459.7 ± 223.9*,Δ	7.5 ± 2.7*,Δ

Compared with the control group *$p < 0.001$; compared with the A group, Δ$p > 0.05$.

dysfunction could also significantly benefit from the early treatment of atorvastatin, which could significantly improve the renal function and reduce the occurrence of proteinuria. It was also recommended by the latest clinical practice guidelines of diabetes and chronic kidney disease by National Kidney Foundation in 2012.

The early CRS patients enrolled into this clinical observation were set as control group, then randomly grouped and treated with valsartan or benazepril combined with atorvastatin, the general information and major treatment programs between two treatment groups had no difference. At the end of follow-up, the blood pressure, blood lipid level and cardiovascular events of the two groups had no significant differences. The results indicated that either ACEI or ARB had no difference in preventing the clinical events.

Currently, clinical evaluation of cardiac functions included 6-min walking test and EF value. BNP is one of the best markers in the prognostic evaluation of heart failure, can quickly and accurately reflect left heart failure, and is the independent predictor of mortality in heart failure patients[14]. Some study[15] showed that the plasma BNP levels of patients with heart failure and renal damage were positively correlated with the extents of heart attack, and could help to determine the prognosis. This study found that most patients achieved the clinical remission, the cardiac functions of these patients were improved significantly. The 6-min walking distance and EF value were increased in both treatment groups, while the serum BNP and 24h urinary protein were decreased. All the results suggested that ACEI and ARB effectively relieved the symptoms, and they could also improve the prognosis of early CRS patients. The research indicated that combined with atorvastatin, valsartan and benazepril exhibited the same effects in improving the function of cardiac. A recent study showed that statins could significantly reduce the mortality of heart failure patients, including the non-ischemic heart failure[7]. Meta-analysis of many clinical trials also showed that statins therapy could reduce the mortality and readmission rate of various reasons-caused heart failure patients[16]. Currently dispute about the statins of the heart failure treatment arose, among which some studies also manifested that the statins treatment effects in the patients with increased hsCRP were positive[17]. The level of hsCRP of CRS patients enrolled into this study was significantly increased. After two years of treatment, the patients showed declining of blood lipid, meanwhile the hsCRP levels were also decreased significantly, indicating that besides the lipid-regulation effect, statins also had such pleiotropia as anti-inflammatory, antioxidant, endothelial function protection, and could regulate the neurohormonal factors[18]. We deduced that regional myocardium and kidney tissues were activated in CRS, RAS inside the blood circulation, and the angiotensin II (Ang II) played the key role, fluvastatin reduced the expression levels of AT1-R mRNA and AT1-R protein in the cultured vascular smooth muscle cells[19], showed that statins could decrease the expression of AT1-R, and ARB could further block AT1-R, thus avoiding the Ang II-promoted myocardial fibrillation, causing the contraction of vascular smooth muscles, increasing the ventricular anterior-posterior loads, vascular and ventricular remodeling, and reducing the synthesis and secretion of aldosterone. Besides the effect of pressure release, ARB protect important target organs as heart and kidney unique. Kawai et al[20] found that the ARB therapy could inhibit the RAS activity, thus significantly decreased the plasma BNP levels, this effect was independent of its antihypertensive effects. Valsartan combined with atorvastatin reduced CRP and BNP, thus playing role in their cardiovascular protective.

Benazepril reduced the transformation of Ang I to Ang II through blocking ACE, and inhibited

all AT1 and AT2 receptor's roles, and strengthened the roles of KKS, decreased the degradation of bradykinin (BK). ACEI could make the levels of Ang-(1 to 7), which were in the other metabolic way of angiotensin and had the diuretic and vasodilator effects, increase, thus, inhibited the ACEI levels inside the blood and local tissues, so Ang I could not be converted into Ang II, and blocked RAS inside the body, mainly inside the cardiovascular tissues, after the treatment, Ang II was declined, when combined with statins, it can reduce the AT1-R expression, together with Statins' pleiotropic effects, thus achieving the stronger target organ protective effects besides the pressure releasing effects.

Because there were similarities in the atherosclerosis and glomerulosclerosis, the beneficial effects of statins in the cardiovascular diseases could also be generalized to the kidney. GREACE study showed that the long-term Statin therapy could significantly improve the renal functions[21]. After two years treatment, this clinical observation found that the blood lipid levels of the treatment group were decreased, indicating that atorvastatin played a protective role in the cardio-renal functions by lowering the blood lipid levels. The decreased serum hsCRP levels of the treatment group showed that beside the role of lipid regulation, statins also had multiple roles such as increasing the activity of the NO synthase, inhibiting the releasing of adhesion molecules by the endothelial cells and macrophages, inflammation-related chemokines and proliferation factors, etc.[22,23]. This effect may help to improve the renal hemodynamics and endothelial functions, inhibit the recruitment of renal monocytes, proliferation and accumulation of mesangial cells, and delay the pathological progress of glomerular filtration. After two years treatment, either the valsartan or benazepril treatment group, compared with the situation before the treatment, the creatinine clearance rates of the two groups were increase by 4 ml/min, the absolute value of the change might seem small, but considering the trend that the creatinine clearance would decrease with the age increasing, it seemed significant, and the difference was also statistically significance. The proteinuria was an important indicator of early kidney damage. Reducing the proteinuria would be benefit in delaying the development of kidney disease. The proteinuria was also a strong independent risk factor in cardiovascular disease[24]. The protective effects of ACEI and ARB in the kidney included hemodynamic and non-hemodynamic effects. (1) hemodynamic effects: reduced the systemic mean arterial pressure, reduced the renal perfusion, meanwhile, the role of expanding the efferent- glomerular arteriole was greater than that of expanding the afferent glomerular arteriole, and thus reduced the intraglomerular pressure. (2) Non-hemodynamic effects: inhibited the proliferation of renal intrinsic cells, reduced the inflammation, improved the glomerular filtration and membrane permeability, etc.[25], thus reduced the excretion of urinary protein, delayed the glomerulosclerosis and tubulointerstitial damage and protected the kidney functions. Combined with statins, the renal protective effects of the 2 groups had no difference.

Apply of statins and valsartan or benazepril, the liver dysfunction, declining of glomerular filtration rate (GFR) and hyperkalemia may occur, this result is different from the currently-known major adverse reactions. So the application process needed to be monitored, and adjusted the dosage according to the basic levels and follow-up fluctuation situations of the patients, these adverse reactions had no difference between the two groups. But the number of the patients that quit the research because of the intolerable cough in the benazepril group was significantly higher than the valsartan group, indicated that the valsartan group had better tolerance than the benazepril group.

Conclusions

The long-term treatment of valsartan or benazepril combined with statins could effectively relieve the symptoms of early CRS patients, and the mechanism may be that valsartan or benazepril can synergic with statins. Under these circumstances, RAAS is blocked more effectively, the hemodynamics and endothelial functions is improved, the inflammation is inhibited, cardio-renal and vascular are protected effectively, the progress of CRS is delayed, meanwhile, the prognosis is improved. However, more specific mechanisms still needed to be further explored.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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