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Nicorandil Decreases Renal Injury in Patients With Coronary Heart Disease Complicated With Type I Cardiorenal Syndrome

Xiaozhi Du, MD, Zhiyong Ma, MD, PhD,† Li Li, MD, PhD,† and Xuezhen Zhong, MD‡*

Abstract: Cardiorenal syndrome (CRS) is a group of disorders in which heart or kidney dysfunction worsens each other. This study aimed to explore the improvement effect of nicorandil on cardiorenal injury in patients with type I CRS. Patients with coronary heart disease complicated with type I CRS were enrolled. Based on the conventional treatment, the patients were prospectively randomized into a conventional treatment group and a nicorandil group, which was treated with 24 mg/d nicorandil intravenously for 1 week. Fasting peripheral venous blood serum and urine were collected before and at the end of treatment. An automatic biochemical analyzer and enzyme linked immunosorbent assay were used to detect B-type brain natriuretic peptide (BNP), serum creatinine (Scr) and cystatin C (Cys-C), renal injury index–kidney injury molecule-1 (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL), and interleukin-18 (IL-18) levels. The left ventricular ejection fraction was measured by echocardiography. All measurements were not significantly different between the nicorandil and conventional treatment groups before treatment (all $P > 0.05$), and BNP, Scr, Cys-C, NGAL, KIM-1, and IL-18 were decreased in the 2 groups at the end of treatment (all $P < 0.05$). Compared with the conventional treatment group, BNP, Scr, Cys-C, NGAL, KIM-1, and IL-18 were more significantly decreased in the nicorandil group (all $P < 0.05$) and left ventricular ejection fraction was more significantly increased ($P < 0.05$). Therefore, nicorandil could significantly improve the cardiac and renal function of patients with type I CRS. This may prove to be a new therapeutic tool for improving the prognosis and rehabilitation of type I CRS.

Key Words: type I cardiorenal syndrome, coronary heart disease, nicorandil, kidney injury molecule-1, neutrophil gelatinase–associated lipocalin

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INTRODUCTION

Coronary heart disease (CHD) has become the primary cause of death worldwide in both developed and developing countries.[1] In China, the mortality rates of CHD in urban and rural residents were 122.04/100,000 and 115.32/100,000, respectively, in 2017.[2] The Global Burden of Disease study reported that ischemic heart disease led to approximately 1.7 million deaths in China in 2016.[3] CHD has become the leading cause of death in the Chinese population and a serious public health problem. In particular, acute coronary syndrome (ACS) is the chief and serious type of CHD, leading to ventricular remodeling and heart failure.[4] Previous studies have also found that patients with ACS have a higher incidence of renal dysfunction.[5,6]

In recent years, the concept of cardiorenal syndrome (CRS) has been widely recognized, including a series of diseases involving the heart and kidney.[7,8] Acute or chronic dysfunction of the heart or kidney may lead to acute or chronic dysfunction of another organ. In 2019, the American Heart Association issued a scientific statement on the classification, pathophysiology, diagnosis, and treatment strategy of CRS, which was divided into 5 subtypes.[8] This is very important for the prognosis of patients with type 1 CRS by early detection and the treatment of renal dysfunction in patients with ACS.

However, traditional laboratory indicators for kidney function, such as blood urea nitrogen and creatinine, are limited in the early diagnosis of acute kidney injury (AKI) because of their low sensitivity and specificity.[9] In addition, diuretic treatment for acute heart failure (AHF) makes the evaluation of renal function more complicated. Recent studies have revealed that markers targeted for renal tubular injury have better early evaluation significance for patients with AKI, especially for patients with AHF, than traditional laboratory indicators. Among them, neutrophil gelatinase–associated lipocalin [neutrophil gelatinase–associated lipocalin (NGAL)], urinary kidney injury molecule-1 (KIM-1), and interleukin-18 (IL-18) are increased in the early stage in patients with AKI and can be used as biological markers of early renal dysfunction.[10,11]

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From the *Department of Emergency, People's Hospital of Huaiyin District, Jinan, China; †Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education and Chinese Ministry of Public Health, Department of Cardiology Qilu Hospital, Qilu Hospital, Shandong University; Jinan, China; and ‡Department of Cardiology, Jinan Central Hospital Affiliated to Shandong University, Jinan, China.

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Correspondence: Xuezhen Zhong, MD, Department of Cardiology, Jinan Central Hospital Affiliated to Shandong University, Jiefang Road 105, Jinan 250013, China (e-mail: zhongxzjn@126.com).

However, the role of these renal tubular injury markers in type 1 CRS has not been clearly studied.

Nicorandil can significantly alleviate the occurrence of angina pectoris,[12] reduce the incidence of cardiovascular events, and improve the prognosis in patients with ACS. In patients with heart failure, nicorandil could reduce all-cause mortality, increase cardiac pump function,[13] and improve left ventricular diastolic function.[14] These protective effects of nicorandil might result from the dual vasodilation of coronary and peripheral arteries to increase coronary blood flow, reduce preload and afterload, and alleviate myocardial injury and cardiac remodeling.[15] In addition, some studies have found that nicorandil can provide additional renal protection for chronic kidney disease or significantly reduce the incidence of contrast-induced nephropathy in patients undergoing coronary angiography or percutaneous coronary intervention.[16] The possible mechanism of nicorandil is the reduction of vascular and renal dysfunction[17] or the neutralization of nephrotoxicity by normalizing the TLR4/MAPK P38/NFκ-B inflammatory cascade.[18] Moreover, oral nicorandil reduced cardiac death in hemodialysis patients undergoing coronary revascularization.[19] Therefore, it is very interesting to study the effect of nicorandil on renal function in patients with type 1 CRS. This study will explore the effect of nicorandil on cardiac and renal function in Chinese patients with type I CRS caused by ACS.

MATERIALS AND METHODS

Subjects

From June 2015 to December 2019, patients with CHD complicated with type I CRS who were hospitalized in the ICU of Huaiyin District People's Hospital of Jinan City were enrolled. Based on their conventional treatment for CHD and HF, the patients were prospectively randomized into a conventional treatment group and a nicorandil group, which was treated with 24 mg/d nicorandil intravenously for 1 week. After admission, all routine examinations were performed, especially echocardiography and measurement of myocardial injury markers and brain natriuretic peptide (BNP) and renal function indexes.

Fasting peripheral venous blood serum and urine were collected before and at the end of nicorandil treatment. There were 23 cases in the control group (15 males and 8 females, 67–89 years old with mean age 77.16 ± 6.57 years) and 22 cases in the nicorandil group (15 males and 7 females, aged 59–89 years, with an average age of 75.48 ± 6.02 years).

This study was approved by the Medical Ethics Committee of Huaiyin District People's Hospital of Jinan City and was conducted in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki. All subjects provided informed consents.

Inclusion and Exclusion Criteria

Type I CRS was diagnosed according to the scientific statement on classification, pathophysiology, diagnosis, and treatment strategy of CRS issued by the American Heart Association: AKI caused by rapid deterioration of cardiac function, manifesting as AHF with or without ACS, accompanied by deterioration of renal function.[8] ACS meets the diagnostic criteria of Chinese ACS diagnosis and treatment guidelines; AHF diagnosis conforms to the 2018 China diagnosis and treatment of heart failure guidelines.[11] AKI was determined according to the 2012 KDIGO clinical guidelines for AKI: within 48 hours, serum creatinine (Scr) increased by greater than 0.3 mg/dL (≥26.5 μmol/L); within 7 days, Scr rose to greater than or equal to 1.5 times the baseline value; or urine output was less than 0.5 mL/(kg · h) for 6 hours.[12]

Exclusion Criteria

Patients with diabetic nephropathy, severe infection, malignant tumor, serious liver disease, and blood system disease were excluded. Other types of CRS were excluded, as follows: type 2 CRS, chronic CRS, and chronic HF leading to CKD; type 3 CRS, acute renocardiac syndrome and AKI leading to AHF; type 4 CRS, chronic renocardiac syndrome and CKD leading to chronic HF; and type 5 CRS, namely, secondary CRS and systemic diseases leading to HF and kidney failure at the same time.

Research Method

Study Protocol

All patients were given conventional basic treatments, including general supportive treatment (oxygen inhalation and maintaining appropriate body position or sedation); cardiotonic, diuretic, vasodilator, antiplatelet, anticoagulation, and improvement of coronary circulation; improvement of prognosis (beta blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/ and aldosterone receptor antagonist); and improvement of renal function and maintenance of water electrolyte balance. In addition, nicorandil was given at 24 mg/6 hours (4 mg/h) every day by intravenous drip in the nicorandil group (nicorandil for injection, 12 mg/bottle, Beijing Sihuan Kebao Pharmaceutical Co, Ltd, Bejing, China) for 1 week. This is a standard dose of nicorandil to treat heart failure in our department according to the drug's instructions (2–6 mg/h). In addition, the dose is in accordance with those in previous studies focused on heart failure (0.05–0.2 mg/kg/h, approximately 3–12 mg/h).[20,21] A pharmacokinetic study of nicorandil in patients with impaired renal function revealed that there was no need to change the nicorandil dose in subjects with different degrees of renal failure.[22]

Measurements

Before and at the end of treatment, 3 mL fasting elbow vein blood was collected, and then serum was separated by centrifugation at 3000 r/min for 15 minutes. Serum Scr, cystatin C (Cys-C), and BNP were detected by a Hitachi 7600-20 automatic biochemical analyzer within 20 minutes. The left ventricular ejection fraction (LVEF) was measured by echocardiography. Before and at the end of treatment, 10 mL urine was collected from the middle part of the morning urine stream, centrifuged for 15 minutes at 2500 r/min, and maintained at −80°C. Urine KIM-1, NGAL, and IL-18 were measured by an enzyme linked immunosorbent assay

TABLE 1. General Data of Patients With Type I CRS

	Conventional Treatment (n = 23)	Nicorandil (n = 22)	*P*
Gender (male/female)	15/8	15/7	0.833
Age (yr)	76.57 ± 6.71	75.77 ± 6.68	0.693
Body mass index (kg/m^2)	24.00 ± 3.26	24.45 ± 2.50	0.604
History of CHD (yr)	20.78 ± 3.42	21.09 ± 4.70	0.802
Diabetes mellitus (yes/No)	15/8	14/8	0.912
Hypertension (yes/No)	13/10	14/8	0.626
β-blocker (yes/No)	14/9	10/12	0.376
ACEI or ARB or ARNI (yes/No)	12/11	13/9	0.767
Spironolactone (yes/No)	9/14	12/10	0.376

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor.

Kit (R & D company, Minneapolis, MN) and a Bio Tek ELX 800 microplate reader according to the kit's instructions.

Statistical Analysis

The SPSS 23.0 statistical software for Windows was used for data analysis. Measurement data are expressed as the mean ± SD ($x \pm s$), and counting data are described by cases and percentages. The independent sample *t* test was used for parameter comparison between 2 groups, the paired *t* test was used for intragroup comparisons before and after nicorandil treatment, the χ^2 test was used for the comparison of counting data, and the Pearson correlation test was used for correlation analysis between factors, and the differences were statistically significant at $P < 0.05$.

RESULTS

Comparison of General Data Between the Nicorandil and Conventional Treatment Groups

There was no significant difference in the age, sex, body mass index, or history of hypertension, diabetes mellitus, or CHD between the nicorandil and conventional treatment groups (Table 1, all $P > 0.05$). All patients were treated with cardiotonic, diuretic, vasodilator, antiplatelet, improvement of coronary circulation, improvement of prognosis, improvement of renal function, and maintenance of water electrolyte balance. β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor-neprilysin inhibitors, and aldosterone receptor antagonists (spironolactone) were not used in any patient, and there were no significant differences between the nicorandil and conventional treatment groups (Table 1, all $P > 0.05$).

Comparison of Cardiac Function and Traditional Renal Function Indexes Between the Nicorandil and Conventional Treatment Groups

There was no significant difference in LVEF, serum BNP, Scr, or Cys-C levels between the 2 groups before nicorandil treatment (Table 2, $P > 0.05$). At the end of nicorandil treatment, the serum levels of BNP, Scr, and Cys-C in the 2 groups were lower than those before treatment (Table 2, $P < 0.05$), and LVEF was increased (Table 2, $P < 0.05$). Compared with conventional treatment, nicorandil treatment significantly decreased BNP, Scr, and Cys-C levels and increased LVEF (Table 2 and Fig. 1, $P < 0.05$).

Comparison of New Renal Injury Markers Between the Two Groups

There was no significant difference in urine KIM-1, NGAL, or IL-18 levels between the 2 groups before

TABLE 2. Comparison of Cardiac Function and Traditional Renal Function Indexes Between the Nicorandil Group and Conventional Treatment Group of Patients With Type I ($x \pm s$)

	Conventional Treatment		Nicorandil	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Systolic blood pressure (mm Hg)	143.17 ± 10.14	127.04 ± 8.95*	144.36 ± 10.00	113.55 ± 4.99*†
Diastolic blood pressure (mm Hg)	77.22 ± 7.50	78.45 ± 7.06	69.83 ± 7.55	64.73 ± 3.74*†
Serum BNP (pg/mL)	7961.39 ± 1007.79	6621.78 ± 1075.08*	7899.54 ± 881.15	3704.64 ± 1061.36*†
LVEF (%)	22.26 ± 3.36	36.04 ± 3.91*	23.91 ± 2.24	43.45 ± 3.29*†
Scr (μmoL/L)	207.12 ± 43.96	187.62 ± 44.69*	220.61 ± 46.39	117.27 ± 13.41*†
Cys-C (mg/L)	3.85 ± 0.29	3.48 ± 0.39*	3.85 ± 0.19	2.64 ± 0.21*†

*Compared with those before treatment, $P < 0.05$.
†Compared with those in conventional treatment, $P < 0.05$.

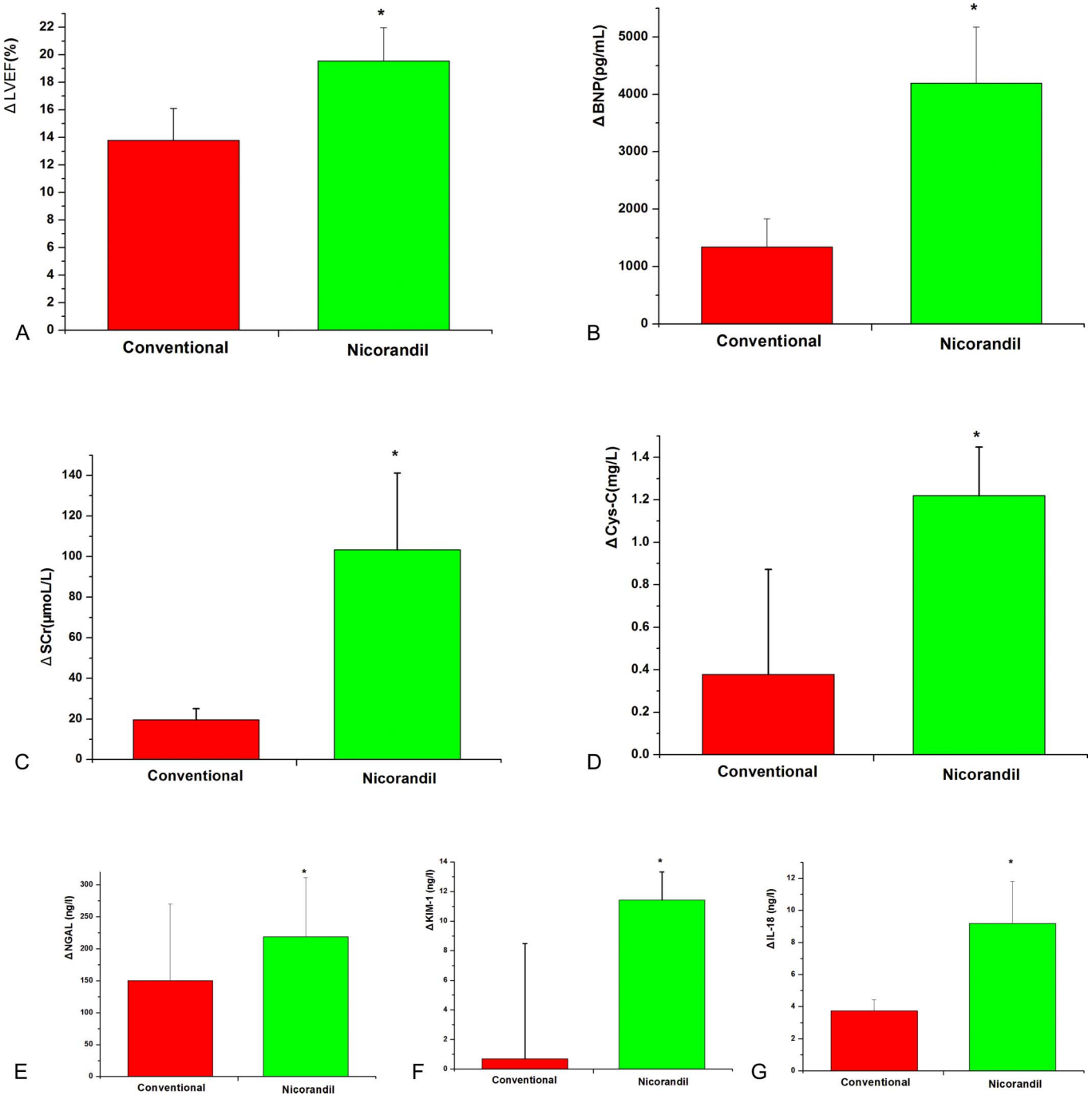

FIGURE 1. Changes in heart function, traditional renal function, and new kidney injury indexes before and after treatment. Compared with the conventional treatment group, the changes in cardiac function indexes (A, LVEF and B, BNP), traditional renal function indexes (C, Scr and D, Cys-C), and new AKI indexes (KIM-1, NGAL, and IL-18" to "E, KIM-1; F, NGAL; G, IL-18) were more significant in the nicorandil group ($P < 0.05$).

nicorandil treatment (all $P > 0.05$). The urine KIM-1, NGAL, and IL-18 levels of the 2 groups after treatment were lower than those before treatment (Table 3, all $P < 0.05$). Compared with conventional treatment, nicorandil significantly reduced urine KIM-1, NGAL, and IL-18 (Table 3 and Fig. 1, $P < 0.05$).

DISCUSSION

Chemically named nicotinamide nitrate, nicorandil, is the first ATP-sensitive potassium channel opener used in clinical treatment.[16] With nitrate-like effects, nicorandil can activate K_{ATP} on vascular smooth muscle, resulting in the outflow of intracellular potassium and an increase in the

TABLE 3. Comparison of New Renal Injury Markers Between the Nicorandil Group and Conventional Treatment Group of Patients With Type I CRS ($x \pm s$)

	Conventional Treatment		Nicorandil	
	Before Treatment	After Treatment	Before Treatment	Before Treatment
Urine KIM-1 (ng/L)	47.90 ± 6.22	47.21 ± 5.71*	49.17 ± 5.56	37.75 ± 5.43*†
Urine NGAL (ng/L)	525.86 ± 153.26	375.51 ± 111.16*	552.08 ± 133.36	333.38 ± 107.39*†
Urine IL-18 (ng/L)	40.85 ± 6.08	37.12 ± 5.94*	39.17 ± 3.48	29.99 ± 4.07*†

*Compared with those before treatment, $P < 0.05$.
†Compared with those in conventional treatment, $P < 0.05$.

negative value of resting membrane potential. Then, the influx of calcium is reduced, leading to the relaxation of vascular smooth muscle and vasodilation.[16,23]

Clinical practices have indicated that nicorandil can dilate coronary vessels, increase coronary blood flow, and relieve coronary vasospasm without affecting heart rate, myocardial contractility, myocardial oxygen consumption, or atrioventricular conduction time.[16–22] Nicorandil is recommended for all types of angina pectoris, especially for spastic angina pectoris. Studies have also confirmed that nicorandil can significantly reduce the incidence of cardiovascular events associated with CHD and improve the prognosis.[24,25]

Further studies have found that nicorandil is also effective in the treatment of HF. Nicorandil can significantly reduce the risk of cardiovascular death in ischemic HF.[24] Harada K et al[26] found that based on standard treatment, intravenous injection of nicorandil (0.2 mg/kg loading dose and subsequent 0.2 mg/kg/h treatment for 24 hours) significantly improved dyspnea and left ventricular diastolic function in emergency patients with AHF syndrome. Based on conventional HF treatment, our study also found that intravenous nicorandil (24 mg/d) could improve LVEF and reduce serum BNP levels, which suggested significant improvement of cardiac function. This effect might result from dilation of the coronary artery and the increase in myocardial blood supply by nicorandil.[25,26] Meanwhile, nicorandil could open mitochondrial ATP-sensitive potassium channels, thus improving myocardial energy metabolism and calcium overload.[24]

Animal experiments further revealed that nicorandil could reduce myocardial hypertrophy and fibrosis in rats with ischemic HF by inhibiting the expression of the Bax gene.[27] In an adriamycin-induced heart failure rat model, nicorandil effectively inhibited adriamycin-induced decreases in heart rate and aortic blood flow and increases in mitochondrial oxidative stress, the cardiac apoptosis signaling pathway, DNA fragmentation, and mitochondrial ultrastructural changes.[28] These results confirmed that nicorandil could effectively improve cardiac function during heart failure. The mechanism involves not only expanding the coronary artery and increasing the myocardial blood supply but also protecting myocardial mitochondrial function and inhibiting cardiomyocyte apoptosis.

In addition to improving heart function, nicorandil was reported to provide additional renal protection for CKD and reduce the incidence of contrast-induced nephropathy in patients undergoing coronary angiography or interventional therapy.[10,17] Therefore, we investigated the effect of nicorandil on renal function and renal injury in patients with type 1 CRS. We found that both conventional standard treatment and additional nicorandil treatment could improve traditional renal function indexes (Scr and Cys-C). However, the decrease in Scr and Cys-C was significantly larger in the nicorandil group, illustrating that nicorandil was able to improve renal function in patients with type 1 CRS. A study found that intravenous nicorandil rather than nitroglycerin could increase the renal artery blood flow velocity.[25] Therefore, nicorandil might improve renal function in patients with type 1 CRS by increasing renal artery blood flow.

A previous animal study confirmed that enalapril or nicorandil alone significantly improved glomerular and tubulointerstitial damage to the rat remnant kidney and reduced oxidative stress, and the combined application of these 2 drugs had an additive effect.[26] In a rat model of unilateral partial ureteral obstruction, nicorandil could effectively reduce serum urea nitrogen and creatinine, increase the activity of renal antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase), reduce leukocyte infiltration and renal tubular dilatation, and inhibit renal tubular injury and renal interstitial fibrosis.[27] Furthermore, we found that nicorandil significantly improved renal tubular injury markers (urine KIM-1, NGAL, and IL-18) compared with conventional treatment. These results indicate that nicorandil can directly improve the renal function of patients with type 1 CRS by protecting renal tubular cells. Previous studies also reinforced this notion. During the treatment of acute decompensated heart failure, there was a lack of significant renal tubular injury (the marker of urinary NGAL) despite AKI.[28] In patients with AHF undergoing aggressive dieresis, renal function worsening was not associated with tubular injury (the markers of urinary NGAL and KIM-1),[29] suggesting that renal tubular injury might not be related to the treatment of heart failure.

Conclusion

The application of nicorandil based on conventional treatment can significantly improve the cardiac and renal function of patients with type I CRS. The possible mechanism is the reduction of cardiac and renal injury reflected by BNP and renal injury markers (urine KIM-1, NGAL, and IL-18). This may prove to be a new therapeutic tool for improving the prognosis and rehabilitation of type I CRS.

Limitations

This is a single center, small sample, and short-term study. A multicenter, prospective study with a larger sample is needed to reveal the role and mechanism of nicorandil for improving renal injury in type I CRS.

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