

Effectiveness of Nicorandil with Trimetazidine with Coronary Heart Disease-Induced Chronic Heart Failure and Its Influence on Cardiac Function in Elderly

LEI WANG, WENQIAN WANG, JINJIN ZHANG*, ZHIKUN ZHAO AND SHASHA WANG

Department of Geriatric Medicine, The Fourth Medical Center of People's Liberation Army (PLA) General Hospital, Haidian, Beijing 100039, China

Wang *et al.*: Effectiveness of Nicorandil with Trimetazidine in Elderly Individuals

To determine the effectiveness of nicorandil in conjunction with trimetazidine on elderly individuals with coronary heart disease-induced chronic heart failure and its influence on the cardiac function. Between January 2018 and December 2022, a retrospective analysis was performed on the data of 248 elderly individuals with coronary heart disease-induced chronic heart failure treated in our hospital. All patients received routine basic treatment, with 110 patients treated with trimetazidine assigned to the control group, and the remaining 138 patients receiving both nicorandil and trimetazidine assigned to the study group. Prior to and after treatment, an evaluation of the cardiac function-related parameters (including left ventricular ejection fraction, left ventricular end-diastolic dimension, and N-terminal pro-brain natriuretic peptide) as well as inflammatory factors (C-reactive protein and interleukin-6) was performed and compared between the two groups. A comparison was made between the two groups regarding efficacy and adverse reactions, followed by logistic regression analysis to examine the risk factors affecting the patient's prognosis. Risk factors affecting the prognosis of patients, as identified by univariate analysis, included age, course of coronary heart disease, New York heart association classification, history of smoking, history of alcoholism, and medication regimen. The prognosis of individuals was found to be influenced by independent risk factors, namely New York heart association classification and medication regimen, as determined by multivariate logistic regression analysis. Effectively treating elderly individuals with coronary heart disease-induced chronic heart failure involves the utilization of nicorandil and trimetazidine in combination. This method not only promotes cardiac function recovery and enhances myocardial cells, but also mitigates inflammatory reactions, all while avoiding the occurrence of increased adverse reactions. Moreover, the prognosis of individuals was influenced by independent risk factors, namely New York heart association classification and medication regimen.

Key words: Nicorandil, trimetazidine, coronary heart disease, chronic heart failure, cardiac function

Coronary Heart Disease (CHD) is a prevalent cardiovascular disorder among the aged population, which is mainly triggered by the imbalance of myocardial energy metabolism, the low pumping function of ventricle and the impaired myocardial structure and function due to long-term hypoxia and ischemia of coronary artery^[1,2]. Heart failure is a major complication of CHD^[3]. In elderly patients with CHD-induced Chronic Heart Failure (CHF), symptoms predominantly arise from an elevation in hemodynamic load, which will damage myocardial structure, cardiac function and myocardium, and the symptoms include

dyspnea, fatigue and urinary retention, which seriously disrupt the normal life of patients^[4,5].

At the current stage, CHD-induced CHF is mainly treated by drugs, which is to delay the deterioration of cardiac function^[6]. Nicorandil is an ATP-sensitive potassium channel opener, with the functions of dilating blood vessels, increasing blood flow and reducing heart load, which is conducive to relaxing blood vessels and smoothing muscle, as well as taking effects in anti-inflammation, stabilizing plaque and improving endothelial function^[7,8]. Trimetazidine is

*Address for correspondence

E-mail: Zjjin2021@163.com

a kind of myocardial energy metabolism drug, which can relieve the inflammatory reaction and protect the myocardium^[9]. The effect of a single drug cannot meet the clinical expectation, but there are still few studies on nicorandil in conjunction with trimetazidine in managing elderly individuals with CHD-induced CHF.

Accordingly, this study explored the effectiveness of nicorandil conjunction with trimetazidine in managing elderly individuals with CHD-induced CHF and its impact on the cardiac function, with the goal of offering evidence-based recommendations for the management of this disease.

MATERIALS AND METHODS

Sample information:

Between January 2018 and December 2022, a retrospective analysis was performed on the data of 248 elderly individuals with CHD-induced CHF treated in our hospital.

Ethical statement:

The Medical Ethics Committee of our hospital granted permission for the implementation of this study.

Inclusion and exclusion criteria:

Inclusion criteria: Individuals who fulfilled the diagnostic criteria of CHD-induced CHF were; typical angina pectoris, myocardial ischemia, orthopnea, paroxysmal nocturnal dyspnea, chest distress, shortness of breath, palpitation, abdominal distension, enlarged border of cardiac dullness, dry and wet rales in both lungs, engorgement of the neck veins, a positive hepatjugular reflux sign, peripheral edema, etc.,^[4] and were diagnosed as CHD-induced CHF by comprehensive judgment such as electrocardiogram and echocardiography; individuals who were aged 65 or older and individuals with detailed clinical data and classified as New York Heart Association (NYHA) II-IV.

Exclusion criteria: Individuals with severe liver or kidney failure, heart failure caused by acute myocardial infarction and other reasons, bronchial asthma, severe infection or drug contraindications; patients who had received coronary artery bypass grafting or percutaneous coronary intervention recently; patients comorbid with severe diseases (such as malignant tumors, etc.) that impact the study and individuals with allergies to the drugs administered in this study.

Sample screening:

Following the criteria-based screening process, a total of 300 patients were initially assessed, resulting in the inclusion of 248 patients who met the specified requirements for this study. All patients received routine basic treatment, with 110 patients treated with trimetazidine assigned to the control group, and the remaining 138 patients receiving both nicorandil and trimetazidine assigned to the study group.

Therapeutic regimen:

Routine medical treatment and symptomatic support, which encompassed interventions like oxygen inhalation, cardiotoxic agents, Beta (β)-receptor blockers, diuretics, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, etc., were provided to patients in both groups. The control group was orally given trimetazidine dihydrochloride tablets (Les Laboratoires Servier Industries, state food and drug administration approval number: H20055465), 20 mg/time, 3 times/d. For the study group, nicorandil tablets (Nipro Pharma Corporation Kagamiishi Plant, Saudi Food and Drug Authority (SFDA) approval number: HJ20160540) were administered orally at a dosage of 5 mg for three times a day, mirroring the dosage of trimetazidine used in the control group. Both groups received treatment for a period of 3 mo.

Outcome measures:

Primary outcome measures: Left Ventricular Ejection Fraction (LVEF), Left Ventricular End-Diastolic Dimension (LVEDD), and N-Terminal pro-Brain Natriuretic Peptide (NT-pro BNP), LVEF and LVEDD were monitored by echocardiography prior to and following treatment. Fasting venous blood was acquired from each individual in the morning prior to and following treatment, and the serum was obtained by 10 min centrifugation with a low-speed centrifuge (3000 r/min). Then the level of serum NT-pro BNP was measured by Enzyme-Linked Immunosorbent Assay (ELISA). In markedly effective, the patient's symptoms essentially vanished, accompanying a two-grade improvement in cardiac function; the patient displayed relief from symptoms and showcased a one-grade improvement in cardiac function was considered as effective and in ineffective, the patient did not meet the above requirements, and even had an aggravating trend. The calculation for the overall response rate involved determining the percentage of cases that displayed marked effectiveness or

effectiveness in treatment, relative to the total number of cases, multiplied by 100 %.

Secondary outcome measures: The serum levels of C-Reactive Protein (CRP) and Interleukin-6 (IL-6) were assessed using an ELISA, both prior to and following treatment; adverse reactions, such as abdominal distension, nausea and vomiting, dizziness, and fatigue, were counted and analyzed; assessment of patient efficacy was conducted, and logistic regression analysis was performed to analyze the risk factors that impacted prognosis.

Statistical analysis:

The analysis compared the measurement data between the two groups utilizing the Statistical Package for the Social Sciences (SPSS) 20.0 software, presented as mean±standard deviation, and employed the Chi-square (χ^2) test for analyzing the count data, with significance defined at $p < 0.05$. The data was visualized into desired graphs using the GraphPad 8 software package. By employing logistic regression, an assessment of the risk factors influencing the prognosis of the patients was performed.

RESULTS AND DISCUSSION

The baseline data comparison between the two groups showed no notable variations in age, gender, Body Mass Index (BMI), duration of CHD, NYHA

classification, smoking history, alcoholism history, and place of residence ($p > 0.05$, Table 1).

Comparing the levels of LVEF, LVEDD, and NT-pro BNP between the two groups prior to and following treatment, no remarkable differences were identified in these levels prior to treatment ($p > 0.05$). However, following treatment, both groups saw a substantial increase in LVEF, along with a notable decrease in LVEDD and NT-pro BNP levels ($p < 0.05$). Further analysis revealed that, following treatment, the study group exhibited a remarkably higher LVEF level ($p < 0.0001$) and lower levels of LVEDD and NT-pro BNP as opposed to the control group ($p < 0.0001$, fig. 1).

Prior to treatment, no noteworthy differences in CRP and IL-6 levels between the two groups was observed ($p > 0.05$). Following treatment, both groups exhibited a considerable reduction in the levels of CRP and IL-6 ($p < 0.0001$), with a more substantial decrease found in the study group compared to the control group ($p < 0.0001$, fig. 2).

The analysis of clinical efficacy revealed a marked disparity in the overall response rate between the two groups, with the control group exhibiting a remarkably lower rate as opposed to the study group ($p = 0.003$, Table 2).

TABLE 1: BASELINE DATA

Factors		Study group (n=138)	Control group	χ^2	p
Age	≥70 y old	50	51	2.603	0.108
	<70 y old	88	59		
Gender	Male	65	45	0.951	0.33
	Female	73	65		
BMI	≥23 kg/m ²	71	60	0.236	0.628
	< 23 kg/m ²	67	50		
Course of coronary heart disease	≥5 y	57	47	0.051	0.822
	<5 y	81	63		
NYHA class	Class II-III	86	65	0.268	0.605
	Class IV	52	45		
History of smoking	Yes	65	41	2.416	0.12
	No	73	69		
History of alcoholism	Yes	45	25	2.95	0.086
	No	93	85		
Place of residence	Rural areas	88	67	0.214	0.644
	Urban areas	50	43		

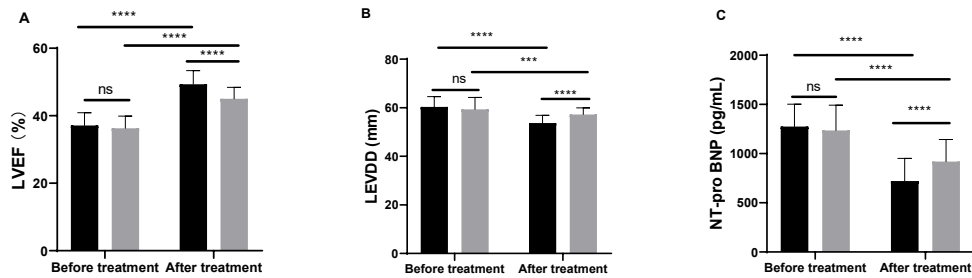


Fig. 1: Comparison of LVEF, LVEDD and NT-pro BNP prior to and following treatment, (A): LVEF level; (B): LVEDD level and (C): NT-pro BNP level

Note: $^{ns}p>0.05$; $^{***}p<0.001$ and $^{****}p<0.0001$, (■): Study group and (□): Control group

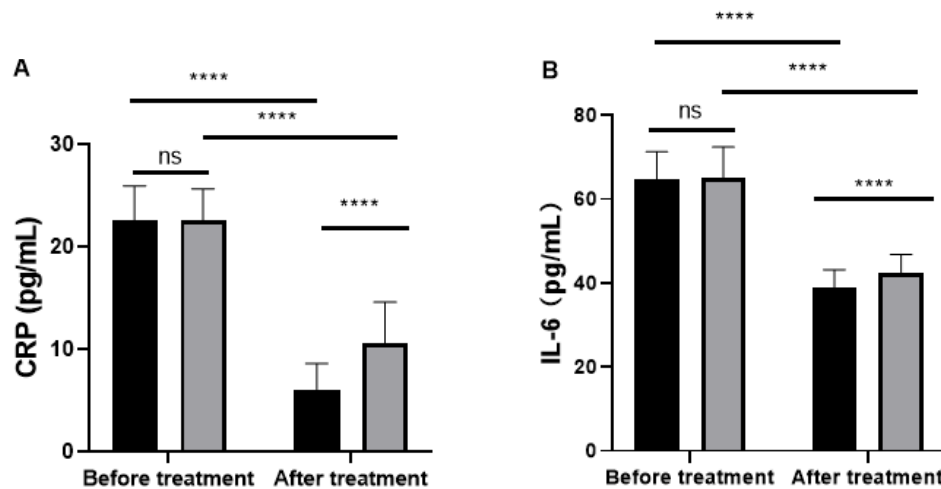


Fig. 2: Comparison of CRP and IL-6 levels prior to and following treatment, (A): CRP level and (B): IL-6 level

Note: $^{ns}p>0.05$ and $^{****}p<0.0001$, (■): Study group and (□): Control group

TABLE 2: COMPARISON OF EFFICACY (n (%))

Group	Markedly effective	Effective	Ineffective	Overall response
Study (n=138)	84 (60.87)	44 (31.88)	10 (7.25)	128 (92.75)
Control (n=110)	49 (44.55)	39 (35.45)	22 (20.00)	88 (80.00)
χ^2	6.559	0.350	8.859	8.859
p	0.010	0.554	0.003	0.003

No noteworthy difference was observed in the total incidence of adverse reactions between the two groups, as revealed by statistical analysis ($p=0.853$, Table 3).

Following treatment, patients who experienced marked effectiveness or effectiveness in their treatment outcome were classified as having a positive prognosis, and were subsequently assigned to the good-prognosis group ($n=216$). Patients who achieved an ineffective treatment outcome were categorized as having a poor prognosis, and were included in the poor-prognosis group ($n=32$). Univariate analysis of the clinical data from the

two groups revealed that age, duration of CHD, NYHA classification, history of smoking, history of alcoholism, and medication regimen were identified as risk factors impacting the prognosis of the patients (Table 4). Subsequent to identification, the indicators that exhibited noteworthy differences were specified (Table 5) and were later examined using multivariate analysis. Independent risk factors influencing the prognosis of the patients were identified as NYHA classification and medication regimen, as per the results of multivariate logistic regression analysis (Table 6).

TABLE 3: INCIDENCE OF ADVERSE REACTIONS (n (%))

Group	Abdominal distention	Nausea and vomiting	Dizziness	Fatigue	Total adverse reaction
Study (n=138)	3 (2.17)	2 (1.45)	1 (0.72)	2 (1.45)	8 (5.79)
Control (n=110)	4 (3.64)	1 (0.91)	1 (0.91)	1 (0.91)	7 (6.34)
χ^2					0.035
P					0.853

TABLE 4: UNIVARIATE ANALYSIS

Factors		Good-prognosis group (n=216)	Poor prognosis group (n=32)	χ^2	P
Age	≥70 y old	78	23	14.771	0.0001
	<70 y old	138	9		
Gender	Male	93	17	1.145	0.285
	Female	123	15		
BMI	≥23 kg/m ²	111	20	1.381	0.24
	<23 kg/m ²	105	12		
Course of coronary heart disease	≥5 y	76	28	31.331	<0.0001
	<5 y	140	4		
NYHA class	Class II-III	139	12	8.438	0.004
	Class IV	77	20		
History of smoking	Yes	85	21	7.861	0.005
	No	131	11		
History of alcoholism	Yes	45	25	16.191	<0.0001
	No	93	85		
Place of residence	Rural areas	138	17	1.378	0.241
	Urban areas	78	15		
Therapeutic regimen	Nicorandil+trimetazidine	125	13	4.073	0.044
	Trimetazidine	90	20		

TABLE 5: ASSIGNMENT

Factors	Assignment
Age	<70 y old=0 and ≥70 y old=1
Course of coronary heart disease	<5 y=0 and ≥5 y=1
NYHA classification	Class II-III=0 and class IV=1
History of smoking	None=0 and yes=1
History of alcoholism	None=0 and yes=1
Medication regimen	Nicorandil+trimetazidine=0 and trimetazidine=1
Prognosis	Good prognosis=0 and poor prognosis=1

TABLE 6: ULTIVARIATE LOGISTIC REGRESSION ANALYSIS

Factors	B	SE	Wald	Df	Sig.	Exp (B)	95 % CI for Exp (B)	
							Lower limit	Upper limit
Age	0.523	0.393	1.777	1	0.183	1.687	0.782	3.642
Course of coronary heart disease	0.333	0.395	0.709	1	0.4	1.395	0.643	3.026
NYHA classification	-1.04	0.479	4.715	1	0.03	0.354	0.138	0.904

History of smoking	0.335	0.401	0.698	1	0.404	1.398	0.637	3.068
History of alcoholism	-0.562	0.491	1.309	1	0.252	0.57	0.218	1.492
Medication regimen	-1.083	0.453	5.703	1	0.017	0.339	0.139	0.824

Note: (SE): Standard Error; (Df): Degrees of Freedom; (Sig.): Significance; (Exp (B)): Exponentiation of the B coefficient and (CI): Confidence Interval

The final stage of CHD, known as CHF, is prevalent among the elderly population with a high incidence^[10]. Without timely treatment, it will aggravate the symptoms of heart failure and even endanger the life of patients, which is not conducive to their prognosis^[11]. With the increasing proportion of the elderly population in society, CHD-induced CHF has become the main reason for admission of the elderly to a hospital, which has brought huge economic burden to the society^[12-14]. Therefore, its treatment is one of the hot issues in clinical research.

At the current stage, the main treatment method for CHD-induced CHF is drug therapy. Nicorandil is a nitrate drug, which can effectively treat angina pectoris of CHD, and its clinical effect is more significant than that of ordinary nitrate drugs, with relatively few adverse reactions and side effects^[15-17]. Trimetazidine is a piperazine derivative, which can directly act on 3-cupric acyl-Coenzyme A (CoA) thiolytic enzyme to inhibit myocardial fat oxidation, improve myocardial oxygen consumption and thus play a protective role^[18]. This study explored the efficacy of nicorandil in conjunction with trimetazidine on elderly individuals with CHD-induced CHF and the influence on the cardiac function.

LVEF, LVEDD and NT-pro BNP are all cardiac function-associated indexes, which can be adopted for evaluating and monitoring the functional state of the heart^[19]. In this study, similar levels of LVEF, LVEDD and NT-pro BNP were observed prior to treatment. Post-treatment, both groups demonstrated a noticeable elevation in LVEF and decrease in LVEDD and NT-pro BNP levels, with the study group displaying a more substantial increase and reductions in comparison to the control group. The findings imply that nicorandil in conjunction with trimetazidine can improve the cardiac function-associated indexes of patients and can take a positive role in promoting the reflux of cardiac ejection and venous blood, body remodeling and cardiac remodeling, thus effectively promoting the recovery of cardiac function and improving cardiomyocytes. CRP is a common inflammatory

marker, and its high level suggests a possible intimal injury and atherosclerosis^[20]. In patients with CHF, the level of IL-6, a pro-inflammatory factor, tends to increase^[21]. The increase of IL-6 may be bound up with myocardial injury, ventricular remodeling and deterioration of cardiac function. Pre-treatment, the CRP and IL-6 levels in both groups were similar in this study. Subsequently, following treatment, both groups experienced a remarkable decrease in CRP and IL-6 levels, with the study group demonstrating a more pronounced decline. It implies that nicorandil in conjunction with trimetazidine can alleviate the inflammatory reaction of patients with CHD-induced CHF more effectively than trimetazidine alone. In this study, no remarkable difference was noted between the two groups in the total incidence of adverse reactions, but the control group exhibited a substantially lower overall response rate compared to the study group. The results imply that nicorandil in conjunction with trimetazidine can effectively manage patients with CHD-induced CHF without increasing adverse reactions. Wu *et al.*^[22] have also found that nicorandil combined with trimetazidine can effectively treat patients with CHD, which align with the results of this research. The analysis of this study revealed that the factors influencing the patients' prognosis included age, course of CHD, NYHA classification, history of smoking, history of alcoholism, and medication regimen. According to the results of the logistics regression analysis, NYHA classification and medication regimen emerged as independent risk factors influencing the patient's prognosis.

Although the research has yielded a number of positive findings, it is not without limitations. Some variations in the study's conclusions may be attributed to the limited sample size. Additionally, further research is necessary to determine the optimal dosages of both drugs, as the current study did not address this aspect.

In summary, nicorandil in conjunction with trimetazidine is effective in treating elderly patients with CHD-induced CHF, which can improve the recovery of the cardiac function, enhance myocardial

cells and relieve inflammatory reaction, without the increase of adverse reactions. Furthermore, independent risk factors impacting patient prognosis include NYHA classification and medication regimen.

Authors' contributions:

Lei Wang and Wenqian Wang have contributed equally to this work.

Conflict of interests:

The authors declared no conflict of interests.

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