Int J Clin Exp Med 2019;12(10):12410-12417
www.ijcem.com /ISSN:1940-5901/IJCEM0093232

Original Article

Effects of nicorandil on cardiac function and interleukin-10 and interleukin-17 levels in elderly patients with chronic heart failure

Xiuying Luo, Honghui Ji, Weiwei Zhang, Aiguo Chong, Bin Hu

Department of Cardiology, The Second Affiliated Hospital (Jiande Branch), Zhejiang University School of Medicine, Jiande, Hangzhou, Zhejiang, China

Received March 2, 2019; Accepted May 10, 2019; Epub October 15, 2019; Published October 30, 2019

Abstract: Objective: The aim of the current study was to investigate the effects of nicorandil on cardiac function and interleukin (IL)-10 and IL-17 levels in elderly patients with chronic heart failure. Methods: This study prospectively analyzed 141 cases of chronic congestive heart failure in elderly patients, randomly divided into two groups. A total of 70 patients were treated with conventional therapy (control group), while 71 patients were treated with conventional therapy in combination with nicorandil (study group). Changes in New York Heart Association (NYHA) grades were used to evaluate therapeutic effects. Changes in cardiac function indicators, including creatinine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), and plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and changes in serum IL-10 and IL-17 levels were measured before treatment and 3 months after treatment. Results: After treatment, the proportion of NYHA class 1 to class 4 patients in the control group was 10.00% (7 cases), 72.86% (51 cases), 17.14% (12 cases), and 0.00% (0 cases). The proportion of NYHA class 1 to class 4 patients in the study group was 25.35% (18 cases), 69.01% (49 cases), 5.63% (4 cases), and 0.00% (0 cases). Decreases in NYHA grades in the study group were more significant than those in the control group ($P<0.05$). Levels of CK-MB, LDH, and NT-proBNP, after treatment, in the 2 groups were significantly lower than those before treatment ($P<0.05$). However, serum levels of CK-MB, LDH, and NT-proBNP in the study group were significantly lower than those in the control group ($P<0.05$). After treatment, the 6-minute walking distance of the study group was also significantly longer than that of the control group. After treatment, IL-10 levels in the 2 groups were increased, to various degrees, compared to levels before treatment ($P<0.05$). IL-17 levels were lower than those before treatment ($P<0.05$). However, serum IL-10 levels in the study group were significantly higher than those in the control group ($P<0.05$), while IL-17 levels were significantly lower than those in the control group ($P<0.05$). Multivariate analysis suggested that age, BMI, heart rate, ejection fraction, and NT-proBNP were independent risk factors for prognosis ($P<0.05$). Conclusion: Nicorandil provides better adjuvant therapy for treatment of elderly patients with chronic heart failure, improving heart function and reducing inflammation.

Keywords: Nicorandil, elderly chronic congestive heart failure, myocardial metabolism, cardiac function, inflammatory factor

Introduction

Chronic heart failure is a common clinical syndrome caused by a variety of cardiovascular diseases. Injury to vital organs can result in shock, poor prognosis, and high mortality rates. Previous studies have reported that patients with chronic heart failure have 5-year survival rates similar to those for malignant tumors [1-3]. Incidence of chronic heart failure increases with age, increasing about 10-fold for every 10 years of age. Therefore, chronic heart failure in elderly patients is an important public health problem [4].

Nicorandil [N-(2-hydroxyethyl) nicotinamide nitrate] is the first clinically available ATP-sensitive potassium channel opener with nitrate characteristics. It can promote potassium efflux, inhibit calcium influx, promote vasodilation, increase blood circulation, and reduce the effects of cardiac preload and afterload [5, 6]. The therapeutic effects of nicorandil in angina pectoris have been clinically proven [7, 8]. In recent years, many studies have reported that nicorandil also has good efficacy in chronic heart failure [9, 10]. However, the specific mechanisms need to be verified. The loss of cardiac compensatory capacity and an increase in inflammatory cyto-

kines are two important processes leading to heart failure. Improving heart function and reducing inflammatory cytokine levels are important in the treatment of heart failure [11, 12].

The current study retrospectively analyzed the therapeutic effects of nicorandil in elderly patients with chronic heart failure, including effects on cardiac function and inflammatory cytokine levels.

Materials and methods

Research objectives

The current study prospectively analyzed 141 cases of chronic congestive heart failure in elderly patients, between April 2015 and February 2018. They were randomly divided into two groups. A total of 70 patients were treated with conventional therapy, such as oxygen, diuretics, and cardiac stress (control group). The other 71 patients were treated with conventional therapy in combination with nicorandil (study group).

Inclusion criteria: Patients met the 2012 Chronic Heart Failure Guidelines [13]; Patients aged 65-79 years, with New York Heart Association (NYHA) grades 2-3; Left ventricular ejection fraction less than or equal to 50%; Mitral blood flow E/A ratio of less than 1; No abnormal bleeding or coagulation abnormalities; No other organ function deficits; Complete medical records were available. Exclusion criteria: Heart failure due to other causes, such as acute myocardial infarction and cardiogenic shock; Presence of valvular arrhythmia, atrial fibrillation, bundle branch block, unstable angina, and other cardiomyopathy; Presence of allergies or contraindications to nicorandil, including glaucoma, patients with severe liver and kidney diseases, patients taking erectile dysfunction therapeutic agents with phosphodiesterase 5 blocking effects, and patients with thyroid disease; Patients with severe infections; Patients with hypokalemia. All patients and family members provided written informed consent and the Medical Ethics Committee approved the current study.

Outcome measures

Changes in NYHA grades were used to evaluate therapeutic effects. Changes in cardiac function indicators, including creatinine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), 6-minute walk experiment, and plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and serum levels of interleukin (IL)-10 and IL-17 were measured before treatment and after 3 months of treatment. Cardiac function indicators were measured using an automatic biochemical analyzer (AU-5800; Beckman Coulter Trading (China) Co., Ltd.), while IL-10 and IL-17 were measured using enzyme-linked immunosorbent assays.

Enzyme-linked immunosorbent assays

Fasting morning peripheral blood was collected. Testing was performed within 1 hour. After centrifugation, serum was used to measure IL-10 and IL-17 levels, as follows. A total of 50 μL of sample assay buffer was added to each well and incubated with 50 μL of serum for 2 hours at room temperature. After incubation, the plate was washed 5 times, 100 μL of biotinylated antibody was added, and the plate was incubated for 1 hour at room temperature. The plate was washed again, 100 μL of labeled horseradish peroxidase was added to the plate, and the mixture was incubated in the dark for 20 minutes. Next, 100 μL of chromogenic substrate TMB was added. The mixture was incubated at room temperature for 20 minutes in the dark. Finally, 50 μL of the stop solution was added. A reading was taken within 15 minutes. Wavelength detection was performed using a microplate reader, determining the maximum absorption wavelength at 450 nm. Three sets of duplicate wells were used and the experiment was repeated 3 times. IL-10 and IL-17 test kits were purchased from Shanghai Jingkang Bioengineering Co., Ltd.

Statistical analysis

SPSS 19.0 (Asia Analytics, formerly SPSS China) was used for data analysis. Count data are expressed as [n (%)] and were compared using χ^2 tests. Measurement data are expressed as mean ± sd. Independent t-tests were used for comparisons between the two groups. Two-way repeated measures analyses with post-hoc Bonferroni's tests were used for comparisons within the same group at different times. $P<0.05$ indicates statistical significance.

Table 1. General information

	Control group (n=70)	Research group (n=71)	X^2/t	P
Sex			0.172	0.678
Man	37 (52.86)	40 (56.34)		
Woman	33 (47.14)	31 (43.66)		
Age (year)	72.31±4.56	71.69±4.38	0.823	0.412
BMI (kg/m^2)	18.83±3.12	18.49±3.28	0.631	0.529
Smoking history [(n%)]			0.059	0.808
Yes	39 (55.71)	41 (57.75)		
No	31 (44.29)	30 (42.25)		
Underlying disease [(n%)]			1.224	0.542
Hypertension	22 (31.43)	26 (36.62)		
Diabetes	18 (25.71)	21 (29.58)		
Other	30 (42.86)	24 (33.80)		
Course of disease (month)	37.25±9.48	38.42±10.13	0.480	0.708
Heart rate (second/minute)	71.32±7.46	72.49±7.58	0.924	0.375
Ejection fraction (%)	35.69±5.37	34.88±5.43	0.890	0.375
K (mmol/L)	4.58±0.62	4.49±0.57	0.898	0.371
Na (mmol/L)	132.46±16.37	136.53±16.19	1.484	0.140
SBP (mmHg)	127.46±11.59	128.55±11.32	0.565	0.573
DBP (mmHg)	77.63±9.64	78.59±9.39	0.599	0.550

Table 2. NYHA score changes after treatment

	Control group (n=70)	Research group (n=71)	z	P
			-2.564	0.010
NYHA1	7 (10.00)	18 (25.35)		
NYHA2	51 (72.86)	49 (69.01)		
NYHA3	12 (17.14)	4 (5.63)		
NYHA4	0 (0.00)	0 (0.00)		

Results

Treatment methods

All patients were treated with beta blockers, diuretics, angiotensin receptor blockers, aspirin, statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor antagonists, depending on their condition. In addition to basic treatment, patients received oral nicorandil (H32026221, Jiangsu Shenlong Pharmaceutical Co., Ltd.) at 5 mg three times a day for 3 months.

Basic information

The 70 patients in the control group included 37 males and 33 females, with an average age of 72.31±4.56 years old. The 71 patients in the study group included 41 males and 31 females, with an average age of 71.69±4.38 years. There were no significant sex or age differences between the 2 groups (P> 0.05). There were no statistical differences in other basic data between the 2 groups, including body mass index, smoking history, disease classification, disease course, heart rate, ejection fraction, serum potassium and sodium, systolic blood pressure, and diastolic blood pressure. (P<0.05) (**Table 1**).

Efficacy analysis

After treatment, the proportion of NYHA class 1 to class 4 patients in the control group was 10.00% (7 cases), 72.86% (51 cases), 17.14% (12 cases), and 0.00% (0 cases). The proportion of NYHA class 1 to class 4 patients in the control group in the study group was 25.35% (18 cases), 69.01% (49 cases), 5.63% (4 cases), and 0.00% (0 cases). Decreases in NYHA grades in the study group were more significant than those in the control group (P<0.05) (**Table 2**).

Changes in cardiac function indicators

There were no significant differences in levels of CK-MB, LDH, and NT-proBNP between the 2 groups before treatment (P>0.05). Levels of CK-MB, LDH, and NT-proBNP in the 2 groups were significantly lower than those before treatment (P<0.05). Moreover, after treatment, serum levels of CK-MB, LDH, and NT-proBNP in the study group were significantly lower than those in the control group (P<0.05) (**Table 3**, **Figure 1**).

Six-minute walk experiment

There were no differences in distances of 6-minute walks between the two groups before treatment. After treatment, the distance of 6-minute walking in the control group was

Table 3. Cardiac functional indices before and after treatment

		Control group (n=70)	Research group (n=71)	t	P
CK-MB (U/L)	Prior treatment	34.19±6.33	33.68±6.48	0.473	0.637
	Post treatment	13.46±2.48*	7.61±1.04*	21.441	<0.001
LDH (U/L)	Prior treatment	284.73±36.86	287.17±34.97	0.403	0.687
	Post treatment	217.64±24.17*	183.24±18.37*	9.523	<0.001
NT-proBNP (pg/ml)	Prior treatment	1742.39±324.17	1802.42±382.62	1.004	0.317
	Post treatment	647.84±102.15*	487.67±89.96*	9.885	<0.001

Note: *significantly higher than that in the same group before treatment (P<0.05).

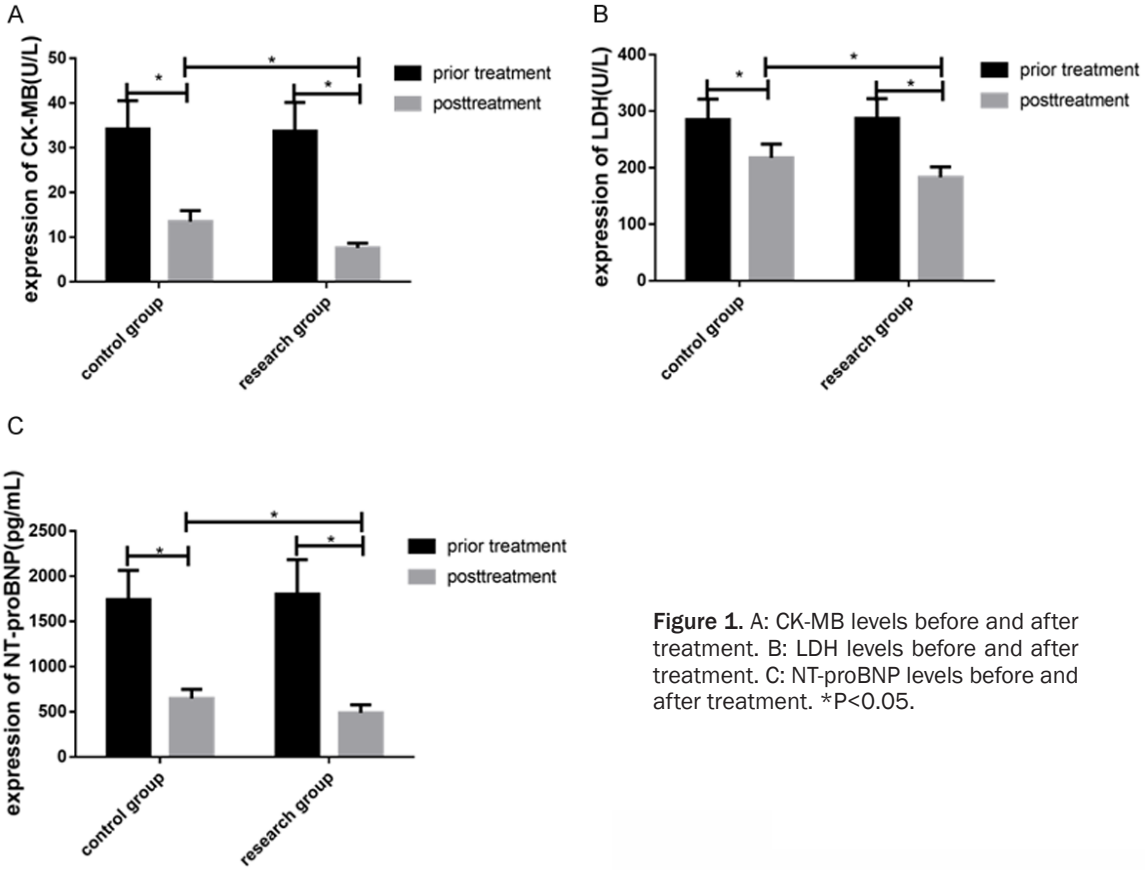

Figure 1. A: CK-MB levels before and after treatment. B: LDH levels before and after treatment. C: NT-proBNP levels before and after treatment. *P<0.05.

(400.42±41.59) m, while the distance in the study group was (463.17±43.75) m, significantly longer than distances before treatment (P< 0.05). Additionally, the distance of 6-minute walking in study group was significantly longer than that in control group after treatment (P< 0.05) (**Table 4**).

Changes in IL-10 and IL-17 levels

There were no significant differences in IL-10 and IL-17 levels between the 2 groups before treatment (P>0.05). After treatment, levels of IL-10 in the 2 groups increased, to various degrees, before treatment (P<0.05). Levels of IL-17 were lower than those before treatment (P<0.05). Moreover, serum IL-10 levels in the study group were significantly higher than those in the control group (P<0.05), while IL-17 levels were significantly lower than those in the control group (P<0.05) (**Table 5**, **Figure 2**).

Risk factors

Clinical characteristics of included patients were considered independent variables, while prognosis (poor prognosis including recurrence and death) was considered a dependent vari-

Table 4. Six-minute walk experiment

	Control group (n=70)	Research group (n=71)	t	P
Prior treatment	312.54±38.62	308.81±39.44	0.569	0.570
Post treatment	400.42±41.59*	463.17±43.75*	8.727	<0.001
t	13.047	22.081		
P	<0.001	<0.001		

Note: *significantly higher than that in the same group before treatment (P<0.05).

Table 5. IL-10 and IL-17 levels before and after treatment

		Control group (n=70)	Research group (n=71)	t	P
IL-10 (mg/L)	Prior treatment	9.12±1.36	9.27±1.29	0.674	0.501
	Post treatment	12.96±2.23*	16.41±2.67*	8.356	<0.001
IL-17 (mg/L)	Prior treatment	9.42±1.28	9.67±1.31	1.150	0.252
	Post treatment	7.88±1.17*	6.12±1.04*	9.474	<0.001

Note: *significantly higher than that in the same group before treatment (P<0.05).

able. Independent risk factors of chronic heart failure were analyzed using logistic multivariate analysis. Results showed that age, BMI, heart rate, ejection fraction, NT-proBNP were independent risk factors for patient prognosis (P<0.05) (**Table 6**).

Discussion

Heart failure is an important cause of death, especially in elderly patients [14, 15]. Therefore, assessment of treatment methods is crucial. In recent years, nicorandil has become relatively popular for treatment of chronic heart failure. However, there are few reports concerning its target of activity. The main features of chronic heart failure are loss of cardiac compensatory capacity, insufficient blood supply, and dysregulated inflammatory response, with promotion of myocardial cell injuries. The current study investigated whether nicorandil improves cardiac function and controls inflammatory response in patients with heart failure.

Medical records of 137 elderly patients with chronic heart failure were examined, according to strict inclusion and exclusion criteria. Comparisons of the basic data in the 2 groups showed no differences, suggesting that the study groups were comparable. Results and conclusions should have credibility. Present results showed that the improvement in NYHA grades was significantly greater in the study group, compared to the control group. Moreover, 6-minute walking distances were significantly longer than those in the control group, suggesting that nicorandil can improve the efficacy of conventional chronic heart failure treatment, as described in similar reports [9, 10]. Improvements in CK-MB, LDH, and NT-proBNP levels in the study group were significantly better than those in the control group, suggesting that nicorandil can improve cardiac function. Nicorandil is a nitrate-based drug that can open the potassium channel in an ATP-dependent manner. It can increase potassium influx, reduce calcium influx, increase resting potential, shorten the action potential cycle, depolarize mitochondrial membranes, promote the production of ATP, and prevent cardiomyocyte apoptosis, thereby alleviating myocardial damage and preventing heart failure [5, 6]. Combined with these findings, the therapeutic effects of nicorandil in chronic heart failure have been confirmed. Results of IL-10 and IL-17 measurements in the 2 groups showed that improvements in inflammatory factors in patients were superior to those in the control group. Results suggest that nicorandil can improve inflammatory response in patients with chronic heart failure. CK-MB, LDH, and NT-proBNP are specific indicators of myocardial injury. CK-MB is less abundant in the serum, accounting for only 5% of all CK. Its sensitivity and specificity for myocardial damage is very high. LDH is involved in energy metabolism of the cardiomyocytes. When myocardial injuries and metabolic abnormalities develop, LDH is released, causing an increase in peripheral blood LDH levels. NT-proBNP is a degradation product of brain natriuretic peptide precursors. Increased ventricular pressure load and volume expansion increase levels of NT-proBNP in peripheral blood. NT-proBNP has a long half-life and is less affected by exogenous brain natriuretic peptides, making it an ideal indicator of cardiac function [16-18]. According to some studies on chronic heart failure, CK-MB, LDH, and NT-proBNP showed different degrees of elevation. Levels decreased after treatment.

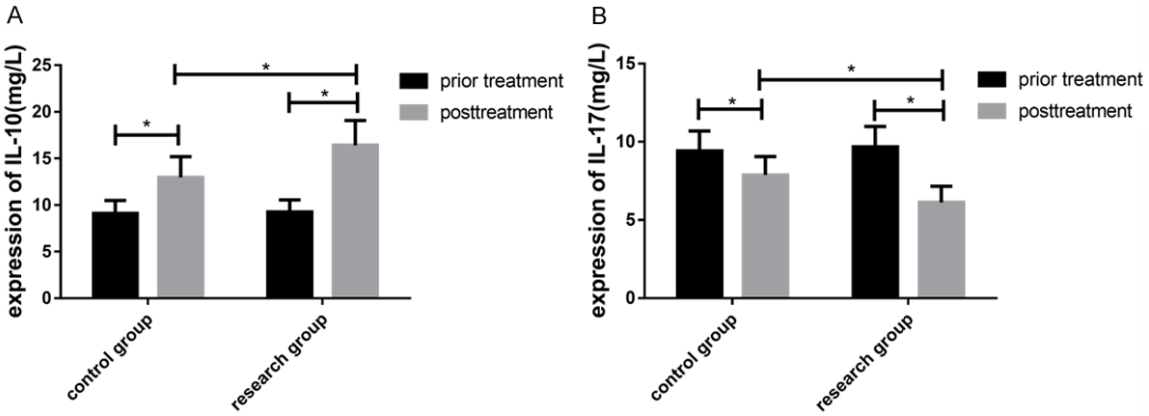

Figure 2. A: IL-10 levels before and after treatment. B: IL-17 levels before and after treatment. *P<0.05.

Table 6. Logistic multi-factor analysis

	OR	95% CI	P
Age	1.038	0.983-1.477	0.014
Gender	1.412	0.495-4.648	0.471
BMI	2.141	0.283-43279	0.022
Smoking	1.032	0.396-3.277	0.723
Hypertension	0.702	0.269-1.712	0.398
Diabetes	0.955	0.322-2.147	0.656
Heart rate	2.236	1.263-5.429	0.014
Ejection fraction	1.583	0.747-3.897	0.032
K^+	0.713	0.325-1.397	0.267
Na^+	1.012	0.973-1.047	0.427
SBP	1.036	0.884-1.125	0.363
DPB	1.253	1.036-1.477	0.315
CK-MB	1.137	0.984-1.385	0.059
LDH	1.062	0.848-1.253	0.139
NT-proBNP	1.689	1.257-3.562	0.006

These results confirm present results to some extent. IL-10 is one of the most important anti-inflammatory cytokines in the body. IL-10 is mainly secreted by helper T2 cell clones. It can inhibit the production of various inflammatory cytokines. Studies have reported that IL-10 can protect against cardiomyocyte injuries [19, 20]. IL-17 is mainly produced by helper T17 cells. IL-17 is an inflammatory cytokine that can cause myocardial cell damage. It plays a role in cardiac remodeling in patients with heart failure [21]. Some studies have reported the anti-inflammatory efficacy of nicorandil in patients with unstable angina, with improvements in inflammatory response in patients with coronary atherosclerosis. These improvements are mainly by reducing the total number of inflammatory cells and inhibiting the release of lymphocytes and macrophages, further inhibiting the release of inflammatory factors [22, 23]. Therefore, the present conclusion that nicorandil can improve inflammatory response in patients with chronic heart failure is made with a certain degree of confidence. In accord with previous studies, it was speculated that nicorandil reduces myocardial cell damage by reducing the total number of inflammatory cells and the release of inflammatory factors. This speculation will be verified in future basic experiments related to cardiomyocyte protection. The current study also analyzed prognostic risk factors of chronic heart failure, finding that age, BMI, heart rate, ejection fraction, and NT-proBNP were independent risk factors for prognosis, in accord with previous relevant report results [24, 25]. However, there were some limitations to the current study. The inclusion of cardiac function indicators and inflammatory indicators was not comprehensive enough. Thus, more clinical randomized experiments are required to validate present conclusions. Due to experimental conditions, the current study was unable to assess disease prognosis. However, it has been reported that nicorandil has the potential to reduce mortality in chronic heart failure [9, 23].

In summary, by improving heart function and reducing inflammation, nicorandil provides adjuvant benefits in the treatment of elderly patients with chronic heart failure.

Acknowledgements

This study was supported by the Hangzhou Key Specialized Disease Project (20150733Q71).

Disclosure of conflict of interest

None.

Address correspondence to: Bin Hu, Department of Cardiology, The Second Affiliated Hospital (Jiande Branch), Zhejiang University School of Medicine, No. 599 Yanzhou Avenue, Jiande, Hangzhou 311600, Zhejiang, China. Tel: 0571-64096782; +86-137-58267101; E-mail: hubbbi@163.com

References

[1] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 891-975.

[2] Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB; CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. Lancet 2016; 387: 453-61.

[3] Sharma A, Lavie CJ, Borer JS, Vallakati A, Goel S, Lopez-Jimenez F, Arbab-Zadeh A, Mukherjee D and Lazar JM. Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. Am J Cardiol 2015; 115: 1428-34.

[4] Hoffman TM. Chronic heart failure. Pediatr Crit Care Med 2016; 17 Suppl 1: S119-23.

[5] Dong YF, Chen ZZ, Zhao Z, Yang DD, Yan H, Ji J and Sun XL. Potential role of microRNA-7 in the anti-neuroinflammation effects of nicorandil in astrocytes induced by oxygen-glucose deprivation. J Neuroinflammation 2016; 13: 60.

[6] Wang S, Fan Y, Feng X, Sun C, Shi Z, Li T, Lv J, Yang Z, Zhao Z and Sun D. Nicorandil alleviates myocardial injury and post-infarction cardiac remodeling by inhibiting Mst1. Biochem Biophys Res Commun 2018; 495: 292-299.

[7] Hirohata A, Yamamoto K, Hirose E, Kobayashi Y, Takafuji H, Sano F, Matsumoto K, Ohara M, Yoshioka R, Takinami H and Ohe T. Nicorandil prevents microvascular dysfunction resulting from PCI in patients with stable angina pectoris: a randomised study. EuroIntervention 2014; 9: 1050-6.

[8] Sani HD, Eshraghi A, Nezafati MH, Vojdanparast M, Shahri B and Nezafati P. Nicorandil versus nitroglycerin for symptomatic relief of angina in patients with slow coronary flow phenomenon: a randomized clinical trial. J Cardiovasc Pharmacol Ther 2015; 20: 401-6.

[9] Kasama S, Toyama T, Iwasaki T, Sumino H, Kumakura H, Minami K, Ichikawa S, Matsumoto N, Sato Y and Kurabayashi M. Effects of oral nicorandil therapy on sympathetic nerve activity and cardiac events in patients with chronic heart failure: subanalysis of our previous report using propensity score matching. Eur J Nucl Med Mol Imaging 2014; 41: 144-54.

[10] Yoshihisa A, Sato Y, Watanabe S, Yokokawa T, Sato T, Suzuki S, Oikawa M, Kobayashi A and Takeishi Y. Decreased cardiac mortality with nicorandil in patients with ischemic heart failure. BMC Cardiovasc Disord 2017; 17: 141.

[11] Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, Alehagen U, Steurer G, Littarru GP; Q-SYMBIO Study Investigators. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. JACC Heart Fail 2014; 2: 641-9.

[12] Dick SA and Epelman S. Chronic heart failure and inflammation: what do we really know? Circ Res 2016; 119: 159-76.

[13] McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012; 14: 803-69.

[14] Sager HB, Hulsmans M, Lavine KJ, Moreira MB, Heidt T, Courties G, Sun Y, Iwamoto Y, Tricot B, Khan OF, Dahlman JE, Borodovsky A, Fitzgerald K, Anderson DG, Weissleder R, Libby P, Swirski FK and Nahrendorf M. Proliferation and recruitment contribute to myocardial macrophage expansion in chronic heart failure. Circ Res 2016; 119: 853-64.

[15] Trøseid M, Ueland T, Hov JR, Svardal A, Gregersen I, Dahl CP, Aakhus S, Gude E, Bjørndal B, Halvorsen B, Karlsen TH, Aukrust P, Gullestad L, Berge RK and Yndestad A. Microbiota-dependent metabolite trimethylamine-N-oxide is associated with disease severity and survival of patients with chronic heart failure. J Intern Med 2015; 277: 717-26.

[16] Haussig S, Woitek F, Mangner N, Leontyev S, Holzhey D, Mohr F, Schuler G and Linke A. Impact of myocardial injury indicated by increased creatinine kinase-myocardial band levels on the outcome after transcatheter aortic valve replacement: results from a prospective single center registry. J Am Coll Cardiol 2017; 69: 1225.

[17] Zhu L, Wei T, Chang X, He H, Gao J, Wen Z and Yan T. Effects of salidroside on myocardial injury in vivo in vitro via regulation of Nox/NF-κB/AP1 pathway. Inflammation 2015; 38: 1589-1598.

[18] Luu B, Leistner DM, Herrmann E, Seeger FH, Honold J, Fichtlscherer S, Zeiher AM and Assmus B. Minute myocardial injury as measured by high-sensitive troponin T serum levels predicts the response to intracoronary infusion of bone marrow-derived mononuclear cells in patients with stable chronic post-infarction heart failure: insights from the TOPCARE-CHD registry. Circ Res 2017; 120: 1938-1946.

[19] Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-preserved trial. Lancet 2003; 362: 777-81.

[20] Tanno M, Kuno A, Yano T, Miura T, Hisahara S, Ishikawa S, Shimamoto K and Horio Y. Induction of manganese superoxide dismutase by nuclear translocation and activation of SIRT1 promotes cell survival in chronic heart failure. J Biol Chem 2010; 285: 8375-82.

[21] Chiurchiù V, Leuti A, Saracini S, Fontana D, Finamore P, Giua R, Padovini L, Incalzi RA and Maccarrone M. Resolution of inflammation is altered in chronic heart failure and entails a dysfunctional responsiveness of T lymphocytes. FASEB J 2019; 33: 909-916.

[22] Lu L, Gao F, Liu ZC and Jing XW. Effect of adjuvant nicorandil therapy on inflammation, plaque stability and platelet function in patients with unstable angina. Journal of Hainan Medical University 2017; 23: 92-96.

[23] Yoshihisa A and Takeishi Y. Beneficial impact of nicorandil on mortality in patients with ischemic heart failure. J Card Fail 2016; 22: S156.

[24] Jong P, Vowinckel E, Liu PP, Gong Y and Tu JV. Prognosis and determinants of survival in patients newly hospitalized for heart failure: a population-based study. Arch Intern Med 2002; 162: 1689-94.

[25] Magalhaes J, Soares F, Noya M, Neimann G, Andrade LT and Correia L. NT-ProBNP at admission versus NT-ProBNP at discharge as a prognostic predictor in acute decompensated heart failure. Int J Cardiovasc Sci 2017; 30: 469-475.