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# Levosimendan Improves Clinical Outcomes of Refractory Heart Failure in Elderly Chinese Patients

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Background:** Levosimendan has been extensively used to treat heart failure (HF) for nearly 10 years, but data on levosimendan used in elderly patients with refractory HF remains limited. This study aimed to investigate the effects of levosimendan on elderly patients with intractable HF.

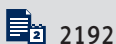
**Material/Methods:** A total of 268 patients with HF (over 70 years, New York Heart Association [NYHA] classification III–IV, LVEF  $\leq 40\%$ , plasma NT-proBNP  $\geq 1000$  pg/mL) received conventional anti-HF therapies for 2 weeks. Such therapies include the limiting of salt intake, increasing myocardial contractility (without levosimendan), inducing urine, antagonizing aldosterone, antagonizing myocardial remodeling, and, if necessary, using antibiotics. Our study included 42 patients without symptoms whose improvement was re-evaluated and presented in NYHA class III–IV, LVEF  $\leq 40\%$ , plasma NT-proBNP  $\geq 1000.0$  pg/mL, and serum creatinine  $< 110.0$   $\mu\text{mol/L}$ . These patients were divided into an experimental groups (n=21, treated with levosimendan) and a control group (n=21, continuously given regular treatment as before). After 1 week, 42 patients were assessed for changes in NYHA classification, LVEF, and NT-proBNP.

**Results:** No severe complications related to levosimendan were noted. Compared with the control group, NYHA classification (I–II: 1 versus 21, III–IV: 20 versus 0,  $P < 0.05$ ) and LVEF ( $30.62 \pm 6.19\%$  versus  $45.83 \pm 5.06\%$ ,  $P < 0.05$ ) were increased, and plasma NT-proBNP was reduced ( $458.35 \pm 193.16$  pg/mL versus  $2921.52 \pm 1395.97$  pg/mL,  $P < 0.05$ ) in the experimental group.

**Conclusions:** Our study showed levosimendan significantly and safely improved clinical outcomes of refractory heart failure in elderly patients.

**MeSH Keywords:** **Aged • Heart Failure • Pain, Intractable • Receptors, Calcium-Sensing**

**Full-text PDF:** <http://www.medscimonit.com/abstract/index/idArt/893580>



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## Background

Congestive heart failure (CHF) is the final endpoint of most cardiovascular diseases and is also a main factor contributing to mortality. In developed countries, 1% to 2% of the adult population is diagnosed with left ventricular dysfunction, but prevalence reaches up to 10% among people over 60-years-old [1]. Mortality in elderly patients is higher than that in younger patients because of several structural and functional changes, such as aortic stiffness and renal impairment [2]. China, the largest developing country in the world, has developed into an aging society because of high morbidity attributed to hypertension, hyperlipidemia, coronary heart disease, and heart dysfunction, which are more common than in developed countries [3].

Molecular biology has been a prominent research focus for the treatment of CHF, which is the key to the prevention or delaying the rapid deterioration of a failing heart [4]. Levosimendan is a new type of  $Ca^{2+}$  sensitizer that can improve myocardial contractility, expand peripheral vessels and the coronary artery, significantly reduce clinical symptoms without increasing myocardial oxygen consumption, and enhance hemodynamics [5]. Levosimendan has been extensively used to treat heart failure (HF) for nearly 10 years. Furthermore, the administration of levosimendan is safe and effective in acute HF [5]. However, data on levosimendan use in elderly patients with refractory HF remains limited.

Given the potential limited data of levosimendan used in elderly patients, in this study we aimed to probe the benefits and safety of levosimendan used only in patients over 70-years-old with intractable HF.

## Material and Methods

This study was approved by the Medical Research Ethics Committee of Chongqing Medical University and was conducted in compliance with the protocol and in accordance with standard institutional operating procedures. All patients enrolled in the study provided their written informed consent.

### Study population

The study followed a prospective, randomized, and open design. HF patients over the age of 70 who had existing symptoms were eligible for this study.

Inclusion Criteria: 1) Symptomatic CHF requiring treatment regardless of previous incidence; 2) No administration of any anti-HF drug within 1–2 weeks; 3) Older than 70 years for both sexes; 4) New York Heart Association classification (NYHA)

of grade III to IV, left ventricular ejection fraction (LVEF) of  $\leq 40\%$  by echocardiography and serum N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) was  $\geq 1000$  pg/mL by blood testing; 5) Willingness to undergo hospitalization.

Exclusion criteria: 1) Uncorrected primary valve diseases or congenital heart disease; 2) Malignant arrhythmia, such as ventricular tachycardia and ventricular fibrillation; 3) Chronic obstructive pulmonary disease; 4) Electrolyte disturbances and hepatic or renal insufficiency (AST, ALT, total bilirubin, or alkaline phosphatase  $>2\times$  the upper limit of normal range; serum creatinine  $>110.0$   $\mu\text{mol/L}$ ; or serum potassium  $>5.0$  mmol/L); 5) Acute heart dysfunction for the first time; 6) Systolic blood pressure  $\geq 180$  mmHg or  $\leq 80$  mmHg and/or diastolic blood pressure  $\geq 110$  mmHg or  $\leq 50$  mmHg, and heart rate  $\geq 180$  bpm or  $\leq 50$  bpm without installation of pacemaker; 7) Anemia of any etiology (Hb  $<10.5$  g/dL) or any other clinically relevant hematological disease; 8) Evidence of any non-cardiac disease likely to worsen HF significantly or shorten life expectancy; 9) Sensitivity or intolerance to levosimendan and/or some other formulation ingredients; 10) Unlikely to comply with the protocol or unable to understand the nature, scope, and possible consequences of the study after full explanation; and 11) Participation in another trial in the month preceding study entry.

All patients were followed up after a minimum of 4 weeks.

### Study design

All recruited patients underwent regular anti-HF treatments for 2 weeks with salt restriction. Treatments included digitalis and/or milrinone, dobutamine to increase myocardial contractility, furosemide and/or hydrochlorothiazide to induce diuresis, spironolactone to antagonize aldosterone, angiotensin converting enzyme inhibitors (ACE-I) and/or angiotensin II receptor antagonists (ARBs) to antagonize myocardial remodeling and improve prognosis, and, if necessary, antibiotics to treat infection (designated as phase I treatment).

After phase I treatment, all patients were re-evaluated by observing NYHA class, LVEF, plasma NT-proBNP, serum creatinine and beta-blocker (such as metoprolol tablets) were considered for from a small dose if their NYHA class was lower than IV. Forty-two patients who exhibited no improvement in HF symptoms were selected. Their NYHA classifications remained from III to IV, LVEF was  $\leq 40\%$ , NTpro-BNP was  $\geq 1000.0$  pg/L, and serum creatinine  $<110.0$   $\mu\text{mol/L}$ . The patients were divided into an experimental group ( $n=21$ ) and a control group ( $n=21$ ) following randomized number rules to receive the next phase of treatment (designated as phase II treatment).

**Table 1.** Clinical characteristics of 268 patients enrolled in the study.

Clinical characteristics	N
Age (years)	74.9±4.3
Gender	
Number of male	146 (53%)
Number of female	131 (47%)
Diseases	
Number of coronary heart diseases	127 (46%)
Number of hypertensive heart diseases	105 (38%)
Number of idiopathic dilated cardiomyopathy	45 (16%)
HF related risk factors	
Number of smoking	58 (21%)
Number of diabetes	53 (19%)
Number of Body Mass Index (BMI) over 30	32 (12%)
Mean systolic blood pressure (mmHg)	132±48
Mean diastolic blood pressure (mmHg)	87±22
Mean heart rate (time/min)	117±62
NYHA	
I-II	0
III-IV	277
LVEF (%)	30.23±5.16
NT-proBNP (pg/mL)	2930.20±1472.35

### Means of using medicine during phase II treatment

The control group, which was similar to phase I treatment, still underwent regular anti-HF treatment with salt restriction, digitalis, dobutamine, frusemide and/or hydrochlorothiazide, spironolactone, and ACE-I and/or ARB. In addition to the aforementioned treatments, the experimental group was intravenously injected with levosimendan (Qilu Medicine Corporation, China; Specifications: 5 mL, 12.5 mg) initially at 12 µg/kg as a primary loading dose (injection time more than 10 min) and then at 0.1 µg/kg/min. After 1 h, the injection speed reached 0.2 µg/kg/min, which was maintained for 23 h [6,7]. In this group, the heart rate and blood pressure were registered at regular intervals. In addition, all patients in this group underwent continuous ECG monitoring.

**Table 2.** Baseline clinical characteristics and NYHA, LVEF, and NT-proBNP of 42 patients after phase I treatment.

Clinical characteristics	N
Age (years)	75.3±4.8
Gender	
Number of male	20 (46%)
Number of female	22 (44%)
Diseases	
Number of coronary heart diseases	16(39%)
Number of hypertensive heart diseases	15 (34%)
Number of idiopathic dilated cardiomyopathy	11 (27%)
HF related risk factors	
Number of smoking	10 (24%)
Number of diabetes	11 (27%)
Number of Body Mass Index (BMI) over 30	5 (12%)
Mean systolic blood pressure (mmHg)	131±46
Mean diastolic blood pressure (mmHg)	84±25
Mean heart rate (time/min)	114±58
NYHA	
I-II	0
III-IV	42
LVEF (%)	30.92±7.13
NT-proBNP (pg/mL)	2952.27±1381.91

### Means of observing parameters during the phase II treatment

After 1 week of phase II treatment, 42 patients were evaluated for the third time according to NYHA classification, LVEF, and NT-proBNP. Some cases had contrasts with their initial values.

### Statistical analysis

Statistical analysis was performed using SPSS 21.0 software. Measurement data is expressed as mean ±SD. Changes in NYHA classification, LVEF and NT-proBNP before and after phase II treatment in the same group were analyzed using the paired-samples t-test, and the comparisons of different groups were

**Table 3.** Comparisons of control and experimental groups in terms of clinical characteristics, NYHA, LVEF, and NT-proBNP before phase II treatment.

Clinical characteristics	Control group	Experimental group	P
Age (years)	74.5±4.3	74.8±4.5	>0.05
Gender			
Male	10 (48%)	10 (48%)	>0.05
Female	11 (52%)	11 (52%)	>0.05
Diseases			
Coronary heart diseases	8 (38%)	8 (38%)	>0.05
Hypertensive heart diseases	7 (33%)	8 (38%)	>0.05
Idiopathic dilated cardiomyopathy	6 (29%)	5 (24%)	>0.05
HF related risk factors			
Smoking	6 (29%)	5 (25%)	>0.05
Diabetes	6 (29%)	5 (25%)	>0.05
Body Mass Index(BMI) over 30	3 (14%)	2 (10%)	>0.05
Mean systolic blood pressure (mmHg)	132±47	133±49	>0.05
Mean diastolic blood pressure (mmHg)	85±24	86±24	>0.05
Mean heart rate (time/min)	117±56	115±53	>0.05
NYHA			
I-II	0	0	>0.05
III-IV	21	21	>0.05
LVEF (%)	30.87±6.27	30.64±6.03	>0.05
NT-proBNP (pg/mL)	2910.50±1490.42	2895.72±1497.51	>0.05

analyzed using the independent-samples t-test. A P value of <0.05 was accepted as statistically significant.

## Results

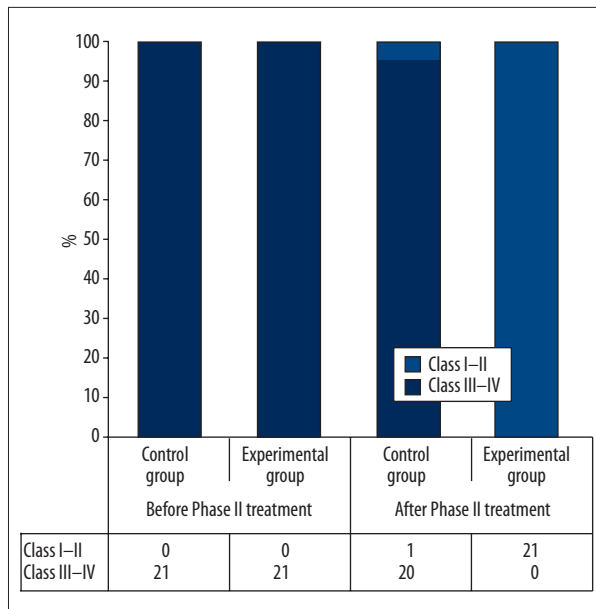
### Patient characteristics

A total of 268 patients from the Cardiovascular Ward or from the Outpatient Department of the Second Affiliated Hospital of Chongqing Medical University from May 2013 to November 2014 were included; 146 (53%) were male and 131 (47%) were female. Among all the patients, 127 were cases of coronary heart diseases, 105 were cases of hypertensive heart diseases, and 45 were cases of idiopathic dilated cardiomyopathy. The clinical characteristics of 268 patients are shown in Table 1.

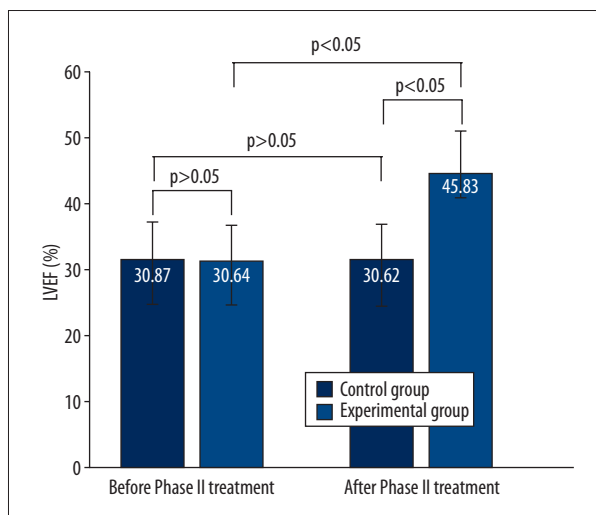
The characteristics of the 42 patients selected from among 268 patients after the phase I treatment are shown in detail in

Table 2. Forty-two patients were selected because they exhibited no improvement in HF symptoms after re-evaluation by observing symptoms, NYHA class, LVEF, plasma NT-pro- BNP, and serum creatinine. We found that among these 42 patients, 16 cases were coronary heart disease (9 men, 7 women), 14 cases were hypertensive heart disease (7 men, 7 women), and 12 cases were idiopathic dilated cardiomyopathy (3 men, 8 women). In addition, NYHA classification remained at III to IV, LVEF ≤40%, NTpro-BNP ≥1000.0 pg/L, and serum creatinine <110.0 μmol/L. These patients can be considered to have intractable HF because they had undergone phase I treatment.

Forty-two patients were divided into the experimental group (n=21) and the control group (n=21) following randomized number rules, and the differences in characteristics between these 2 groups had no statistical significance. Comparisons of the clinical characteristics of the control and experimental groups are shown in Table 3.



**Figure 1.** Changes of NYHA in control and experimental group before and after phase II treatment.

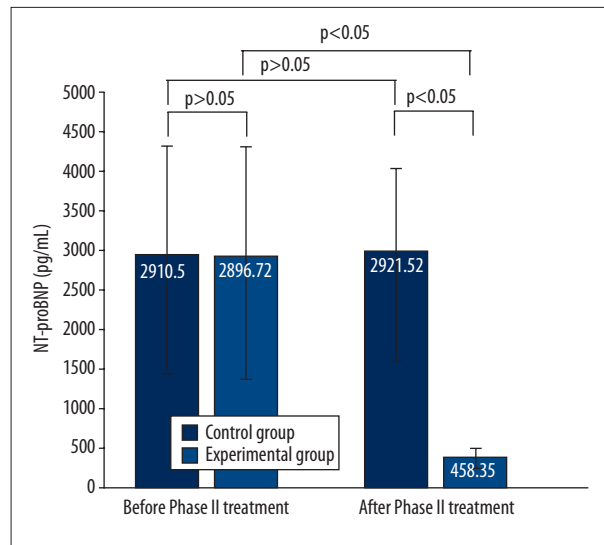


**Figure 2.** Comparison of LVEF within control group or experimental group, between control group and experimental group before and after phase II treatment, respectively.

**Table 4.** Comparisons of the control group and experimental group based on NYHA class, LVEF, and NT-proBNP after phase II treatment.

	NYHA class		LVEF (%)	NT-proBNP (pg/mL)
	I-II (n)	III-IV (n)		
Control group	1	20	30.62±6.19	2921.52±1395.97
Experimental group	21	0	45.83±5.06	458.35±193.16*

\*  $P < 0.01$ , compared with control group.



**Figure 3.** Comparison of NT-proBNP within control group or experimental group, between control group and experimental group before and after phase II treatment, respectively.

### Clinical outcomes

Compared with treatment before phase II, NYHA classification and LVEF in the experimental group after phase II treatment was significantly increased and NT-proBNP was significantly decreased but only 1 case in the control group showed improvement in NYHA classification (Figures 1–3). Compared with the control group, NYHA classification, LVEF and NT-proBNP were significantly improved in the experimental group. The difference between the experimental and control groups were statistically significant at  $P < 0.05$  (Table 4).

### Complications related to Levosimendan

In the experimental group, 21 patients received levosimendan. These patients tolerated levosimendan well and exhibited no complications such as low or high blood pressure, arrhythmia, or aggravation of HF.

## Discussion

The main findings of this prospective, open, controlled, and randomized study were: 1) Levosimendan is associated with a significant improvement in heart function in elderly patients with intractable HF compared with digitalis, milrinone, and dobutamine. 2) The improvement in heart function attributed to levosimendan occurs within a short period of time. 3) Levosimendan is well-tolerated and safe for elderly patients.

CHF is a common ailment and is more prevalent in the elderly. Three main factors may explain this phenomenon: 1) aging-related biological factors; 2) prolonged exposure to cardiovascular risk factors during aging; 3) comorbid conditions associated with aging [8,9]. Pathophysiologies in elderly patients have their own particularities: due to the higher prevalence of complications of movement-related disorders (such as arthropathy, hemiplegia) or because of the hypoposia, daily activities are less in elderly patients, which make symptoms of HF become inconspicuous. Additionally, hypoxemia is more severe in elderly patients because of respiratory dysfunction, lower output, and blood gas exchange abnormalities. Besides, retrograde degeneration of sinus or conduction tissue can result in indistinctive heart rate response to HF in elderly patients [10–12]. CHF in elderly patients deteriorates to acute and severe HF sooner than in non-elderly men. Therefore, therapy in elderly patients must be individualized with aging-specific changes in physiology, drug metabolism, drug pharmacokinetics and tolerance, comorbidities, and polypharmacy, and drug-drug interactions must be taken into consideration [13–15].

In this study, all observed subjects (268 patients) were elderly patients with HF. The patients regularly received anti-HF therapy during phase I treatment. This procedure is termed the “washout period”, which is very important. After the “washout period”, 42 patients with true refractory HF were divided randomly into control and experimental groups for phase II treatment. Referring to Table 3 and Figures 1–3, there were no significant differences in clinical characteristics between the 2 groups before phase II treatment, but the outcomes of NYHA class, LVEF, and NT-proBNP in the experimental group were better than in the control group after phase II treatment, which suggests: 1) Levosimendan was effective in treating true refractory HF in elderly patients; 2) Levosimendan protective in elderly patients; 3) The time needed for levosimendan to take effect was not overly long. We observed this effect within 1 week and because the phase II treatment was short, no ethics problems were presented.

As mentioned above, there were many pathophysiologic particularities in elderly patients, especially in the case of refractory HF. In that situation, cardiac troponin C (cTnC) is insensitive to  $Ca^{2+}$ , so pharmacotherapies such as inhibiting sodium-potassium

ATPase on epicyte to increase the concentration of  $Ca^{2+}$  (e.g., digitalis), or activating adenylate cyclase to increase myocardial intracellular cAMP (e.g., dobutamine), or inhibiting phosphodiesterase, which causes cAMP to decompose more slowly to increase myocardial intracellular cAMP (e.g., milrinone) thus preventing the other drugs from promoting myocardial contractility. However, levosimendan and a  $Ca^{2+}$  sensitizer can be combined with cTnc for the greater sensitivity of the contraction protein to  $Ca^{2+}$ . Even at the same or lower  $Ca^{2+}$  concentration, levosimendan can transform the conformation of myosin and activate excitation–contraction coupling, finally resulting in myocardial contraction [16]. A unique advantage of levosimendan is that it enhances myocardial contractility without increasing myocardial oxygen consumption [17], which was why levosimendan benefited true refractory HF in elderly patients. A meta-analysis of randomized controlled trials on levosimendan versus dobutamine in critically ill patients showed that the former is associated with a significant improvement in mortality [18]. Levosimendan can also induce changes in heart and blood vessels, which means levosimendan has beneficial effects on coronary circulation, pulmonary circulation, and peripheral circulation [19]. Moreover, levosimendan can be used with ACE-I and  $\beta$  receptor blockers, which are all essential drugs used for anti-CHF treatment [20,21].

One similar study has ever been reported previously in China [22]. However, enrolled patients in that study were over 65 years (not over 70 years old) and there were no comparisons of control and experimental groups in terms of clinical characteristics, NYHA, LVEF, or NT-proBNP before phase II treatment, with no safety or complications taken into consideration. The observation period of phase II treatment in that study was only 3 days, which we think was not long enough to produce all relevant results, especially complications. In this study we noticed that several patients' symptoms improved after 3 days.

## Study limitations

The major limitation of this study is the small population size. The relatively short follow-up of the experimental group is another limitation; thus, we did not determine if levosimendan could improve the long-term prognosis. In addition, the echocardiographic description of the supposed function related to the levosimendan was too simple and we focused only on LVEF, ignoring factors such as diastolic function and the left ventricular dimension.

## Conclusions

In this study we observed that levosimendan could significantly and safely improve NYHA classification and LVEF, as well as significantly reduce plasma NT-proBNP in elderly patients with

intractable HF. The results suggest that in elderly patients with CHF, especially those patients who had an acute exacerbation of advanced heart failure and did not qualify for conventional anti-CHF treatments, levosimendan would be an option.

### Conflict of interest

None.

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