Acta Cardiol Sin 2019;35:585–591
Original Article
doi: 10.6515/ACS.201911_35(6).20190327A

Cardiomyopathy & Heart Failure

Effects of Levosimendan on Right Ventricular Function in Patients with Acute Decompensated Heart Failure

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Background: To investigate the effects of levosimendan on right ventricular (RV) function in patients with acute decompensated heart failure (ADHF).

Methods: Patients with ADHF admitted from January 2017 to October 2017 were enrolled in this study. The patients were randomized to receive 24-h intravenous levosimendan or placebo. Echocardiographic examinations were performed and the parameters were compared. Epidemiological data were recorded and compared before and after treatment. Major adverse cardiac events during hospitalization and during 1-month follow-up were compared.

Results: The baseline characteristics were comparable. After 24-h infusion of levosimendan and placebo, the left ventricular ejection fraction and S′ were significantly increased in the levosimendan group compared with the control group (both $p < 0.05$). The E value in the levosimendan group significantly decreased (75.38 ± 8.32 vs. 88.21 ± 10.36, $p < 0.0001$), and E/e′ significantly increased in the control group (19.61 ± 6.52 vs. 27.58 ± 8.22, $p < 0.0001$). The levels of right ventricular fractional area change (24 ± 3 vs. 20 ± 2, $p < 0.0001$) and tricuspid annular plane systolic excursion (1.56 ± 0.36 vs. 1.38 ± 0.21, $p < 0.0001$) were significantly higher in the levosimendan group than in the control group. After treatment, the values of systolic pulmonary artery pressure (SPAP) decreased in both groups (both $p < 0.05$), and the value of SPAP in the levosimendan group was lower than that in the control group (47.22 ± 5.6 vs. 55.85 ± 7.41, $p < 0.0001$). After 1-month follow-up, there was no significance in readmissions due to recurrent heart failure.

Conclusions: Levosimendan seems to provide more beneficial effects among patients with ADHF to improve RV function, along with a decrease in pulmonary pressure.

Key Words: Acute decompensated heart failure • Echocardiography • Levosimendan • Right ventricular function

INTRODUCTION

Heart failure (HF) represents a major source of morbidity and mortality.[1,2] Although the management of heart failure has improved, acute decompensated heart failure (ADHF) still remains a highly mortal and morbid disease.[3] Right ventricular (RV) failure is associated with higher mortality rates than left ventricle failure, and optimal RV support is desirable.[4,5] Several inotropic agents are currently available and widely used, however their limitation is the tendency to increase mortality and risk of arrhythmias.[6] The therapeutic utility of levosimendan has been documented in several studies, and its positive effect on systolic left HF is well-known due to a triple

Received: May 12, 2018 Accepted: March 27, 2019
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mechanism of action: calcium channels in cardiac myofilaments, opening of adenosine triphosphate (ATP)-sensitive potassium channels in smooth muscle cells, and ATP-sensitive potassium channels of the mitochondria of cardiac cells. However, only a few studies have evaluated the effects of levosimendan on RV function.[7-9] In this study, we aimed to investigate the effects of levosimendan on RV function in patients with ADHF.

PATIENTS AND METHODS

Study population

Patients with ADHF with New York Heart Association class III or IV symptoms and left ventricular systolic dysfunction admitted to our hospital from January 2017 to October 2017 were enrolled in this single-center, randomized, controlled, open-label study. Patients with a left ventricular ejection fraction (LVEF) < 45% with tricuspid regurgitation detected by echocardiography were included in the study. The exclusion criteria were: pregnancy and lactation, hypersensitivity against levosimendan or any of its metabolites, severe renal failure (creatinine > 2.5 mg/dl), hepatic failure, systolic blood pressure < 85 mmHg, history of ventricular tachycardia or ventricular fibrillation, second or third degree atrioventricular blocks, heart failure caused by restrictive or hypertrophic cardiomyopathy, or uncorrected stenotic valvular disease.

Patient enrollment was carried out according to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of the Second Hospital of Hebei Medical University. Written informed consent was obtained from each patient before his/her participation.

Clinical treatment

Following their referral to the hospital, the patients were randomized to receive 24-h intravenous levosimendan or placebo. Levosimendan was administered as a 10-min intravenous bolus infusion at 6–12 μg/kg, followed by a continuous 24-h infusion at 0.1 μg/kg/min. The infusion was maintained at a constant rate for 24 h unless the patient had a major cardiovascular event or a serious adverse reaction. Treatment with placebo was started with a continuous 24-h infusion of normal saline with similar volume. Other drugs including angiotensin I-converting enzyme inhibitors (ACEIs)/angiotensin II receptor antagonists (ARBs), β-blockers, aldosterone receptor antagonists, diuretics, digitalis, and vasodilators were administered according to current guidelines.

Measurement of heart function

Echocardiographic examinations were performed using ultrasound equipment (GE-Vivid 4 with a 3.5 MHz transducer; GE, Milwaukee, WI, USA) at baseline and after 24 h of inotrope therapy in both groups. The measurements were then evaluated by an independent echocardiography specialist who was blinded to the study plan and clinical status of both groups. Conventional echocardiography was performed, including M-mode and two-dimensional echocardiography. The left ventricle end diastolic diameter (LVEDD), LVEF and right ventricular fractional area change (RVFAC) were measured.[10] The tricuspid annular plane systolic excursion (TAPSE), as a measure of RV base-to-apex shortening during systole, was recorded on M-mode under two-dimensional echocardiographic guidance, and was averaged for five beats in sinus rhythm.[7] In the apical four-chamber view, a 5-mm sample volume of the pulsed wave Doppler was placed on the tricuspid annulus at the place of attachment of the anterior leaflet of the tricuspid valve. The tricuspid annular peak systolic velocity (S′), peak early mitral in flow velocity (E), and mitral valve ring myocardial diastolic early peak velocity (e′) were measured as centimeter per second. S′, E and A velocities were measured from three consecutive cardiac cycles and averaged. The ratio of early to late diastolic tricuspid annular velocities was also calculated. The systolic pulmonary artery pressure (SPAP) was determined as follows. After tricuspid regurgitation had been localized with Doppler color flow imaging, the peak flow velocity of the transtricuspid jet was measured using continuous wave Doppler, and the pressure gradient between the RV and the right atrium was calculated using the modified Bernoulli equation.[11] SPAP was estimated by adding mean right atrial pressure, as estimated by the diameter of the inferior vena cava and its respiratory variation, to the pressure gradient between the RV and atrium.[12] Respiratory collapse of the inferior vena cava was carefully evaluated, and less than 50% change in the diameter was considered to indicate high right atrium pressure.

Epidemiological data on age, sex, previous treatment, heart rate, blood pressure, levels of B-type natriuretic peptide (BNP) as well as changes in body weight were recorded and compared before and after treatment. Urine output was monitored during treatment. Major adverse cardiac events (MACEs) during hospitalization and during 1 month of follow-up were compared.

Endpoint definitions

The primary endpoint was defined as the RV function, which was measured as the value of S′. The second endpoint was defined as the incidence of MACEs.

Statistical analysis

Previous studies[3,7] have shown that the value of s′ could recover to normal. According to the value of s′ measured by echocardiography, normal RV function was defined as s′ greater than or equal to 10 cm/s. Therefore, for a test performance of 0.8 and a type of error of 0.05, 17 patients per group were required. Considering that some patients would become lost to follow-up, at least 20 cases per group were required.

SPSS 19.0 statistical software was used for all calculations. Continuous variables were reported as means ± standard deviation and were compared using the unpaired t-test for normally distributed values and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were expressed as absolute or relative frequencies and were compared using the chi-square test or Fisher's exact test, as appropriate, for the cell frequencies. Multivariate analysis of repetitive measures ANOVA was used to compare differences in the characteristics of echocardiography and BNP level before and after the procedure in each group. $p < 0.05$ was considered to be statistically significant.

RESULTS

From January 2017 to October 2017, 69 cases had ADHF and were administered to our department. Three cases with renal dysfunction, 2 cases who refused to participate and 5 cases without tricuspid regurgitation detected by echocardiography were excluded, and the remaining 59 cases were enrolled in this study. All of the patients enrolled in this study were randomly divided into a levosimendan group (n = 30) and control group (n = 29) (Figure 1, Table 1).

Baseline characteristics between the two groups

The baseline characteristics are shown in Table 1. There were no significant differences between the two groups in epidemiological data, results of laboratory examinations and medical treatments (all $p > 0.05$).

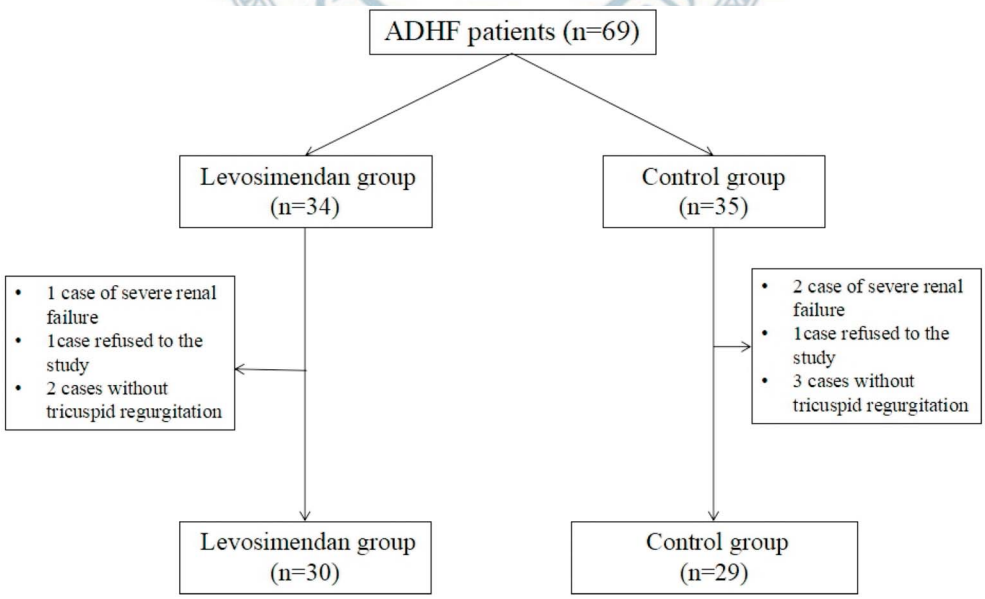

Figure 1. *Patients' selection flow diagram. ADHF, acute decompensated heart failure.*

Table 1. Comparison of baseline characteristics between the two groups

	Levosimendan (n = 30)	Control (n = 29)	p value
Age (yr.)	65.73 ± 13.84	65.66 ± 13.65	0.983
Male-n (%)	21 (70)	20 (69)	0.931
Weight (kg)	67.05 ± 15.93	71.52 ± 17.15	0.304
BMI (kg/m^2)	24.30 ± 5.22	24.93 ± 4.46	0.620
Cause			0.712
Ischmia, n (%)	20 (66.7)	18 (62.1)	
Non-ischmia, n (%)	10 (33.3)	11 (37.9)	
Hypertension, n (%)	15 (50)	15 (51.7)	0.895
Diabetes, n (%)	15 (50)	9 (31.0)	0.138
NYHA classification			0.839
III	15 (56.7)	15 (62.0)	
IV	13 (43.3)	11 (38.0)	
Systolic BP (mmHg)	122.70 ± 20.56	119.17 ± 21.00	0.517
Diastolic BP (mmHg)	73.70 ± 12.49	75.45 ± 13.91	0.613
Heart rate (beat per minute)	84.67 ± 20.28	87.03 ± 24.91	0.690
Serum creatinine (μmol/L)	109.41 ± 40.04	105.45 ± 35.06	0.688
Hemoglobin (g/L)	128.07 ± 18.53	105.45 ± 35.06	0.267
cTnI (ng/ml)	0.59 (0.06, 0.97)	0.37 (0.05,1.02)	0.410
BNP (pg/ml)	1136.05 (545.12, 2043.19)	1409.41 (1168.75, 2069.99)	0.144
Total cholesterol (mmol/L)	3.86 ± 1.03	3.59 ± 0.59	0.218
LDL-C (mmol/L)	2.43 ± 0.79	2.17 ± 0.46	0.130
Aspirin, n (%)	17 (56.7)	14 (48.3)	0.519
Clopidogrel/ticargrelor, n (%)	15 (50)	8 (27.6)	0.078
Beta blocker, n (%)	27 (90)	20 (69)	0.057
ACEI/ARB, n (%)	20 (66.7)	16 (55.2)	0.365
Spirolactone, n (%)	28 (93.3)	26 (89.7)	0.612
Diuretics, n (%)	26 (86.7)	24 (82.8)	0.731
Digitalis, n (%)	10 (33.3)	11 (37.9)	0.712
Nitrate, n (%)	18 (60)	16 (55.2)	0.708
Oral anticoagulants, n (%)	10 (33.3)	8 (27.6)	0.632
Statins, n (%)	19 (63.3)	15 (51.7)	0.367

ACEI/ARB, angiotensin I-converting enzyme inhibitor/angiotensin II receptor antagonists; BMI, body mass index; BNP, B-type natriuretic peptides; BP, blood pressure; cTnI, troponin I; LDL-C, low density lipoprotein cholesterin.

Changes in RV function detected by echocardiography

The heart function was similar between the two groups before treatment. After 24-h infusion of levosimendan and placebo, the LVEF [(35.77 ± 8.25)% vs. (33.59 ± 5.76)%, $p < 0.05$] and S′ (10.43 ± 1.28 cm/s vs. 9.53 ± 1.11 cm/s, $p < 0.05$) significantly increased in the levosimendan group compared with the control group. The value of E in the levosimendan group significantly decreased (75.38 ± 8.32 cm/s vs. 88.21 ± 10.36 cm/s, $p < 0.0001$), and E/e′ significantly increased in the control group (19.61 ± 6.52 vs. 27.58 ± 8.22, $p < 0.0001$). The levels of FAC [(24 ± 3)% vs. (20 ± 2)%, $p < 0.0001$] and TAPSE (1.56 ± 0.36 mm vs. 1.38 ± 0.21 mm, $p < 0.0001$) were significantly higher in the levosimendan group than those in the control group. After treatment, the value of SPAP significantly decreased in both groups (both $p < 0.05$), and the value of SPAP in the levosimendan group was significantly lower than that in the control group (47.22 ± 5.6 mmHg vs. 55.85 ± 7.41 mmHg, $p < 0.0001$). All of the data are shown in Table 2.

Clinical data after treatment and at 1-month follow-up

After 24 h of treatment, the urine discharge in the levosimendan group was more than that in the control

group (1923 ± 285 ml vs. 1761 ± 256 ml, p = 0.026), and the level of BNP was lower than that in the control group (p = 0.005). The levels of systolic blood pressure, diastolic blood pressure and heart rate decreased compared to the baseline levels, however no significant differences were found between the two groups. The values of serum creatinine were similar after treatment, and there were no significant differences in death and hospital duration. After 1 month of follow-up, there was no significance in readmission due to recurrent heart failure (Table 3).

DISCUSSION

Levosimendan is a novel positive inotropic agent used for acute systolic left heart failure. The drug exerts a positive inotropic effect by increasing the calcium sensitivity of cardiac troponin C without increasing intracellular calcium concentrations.[13] Although its useful effects in systolic left heart failure are well-known, limited data are available on the utilization in right heart failure. In this study, we investigated the effects of levosimendan on RV function in patients with ADHF, and we found that levosimendan could improve RV function, including S', FAC and TAPSE.

In this study, we enrolled patients with both ischemic cardiomyopathy and dilated cardiomyopathy, and some of them also had acute coronary syndrome. This may be due to potential differences in the use of clopidogrel, as well as differences in the level of hemoglobin. All medications were used according to the basic

Table 2. Changes of right ventricular functions detected by echocardiography

	Baseline		After treatment	
	Levosimendan (n = 30)	Control (n = 29)	Levosimendan (n = 30)	Control (n = 29)
LVEDD (mm)	62.39 ± 5.27	63.81 ± 6.14	61.58 ± 5.46	63.63 ± 5.29
LVEF (%)	31.20 ± 6.32	33.59 ± 5.76	35.77 ± 8.25*†	32.10 ± 5.08
E (cm/s)	87.15 ± 10.03	85.09 ± 9.88	75.38 ± 8.32#†	88.21 ± 10.36
e' (cm/s)	4.05 ± 0.96	3.90 ± 0.85	4.12 ± 0.95*	3.26 ± 0.74†
E/e'	23.63 ± 5.22	23.38 ± 4.97	19.61 ± 6.52#	27.58 ± 8.22†
S' (cm/s)	9.48 ± 1.06	9.31 ± 0.93	10.43 ± 1.28*†	9.53 ± 1.11
FAC (%)	21 ± 2	20 ± 3	24 ± 3#†	20 ± 2
TAPSE (mm)	1.35 ± 0.21	1.36 ± 0.30	1.56 ± 0.36#†	1.38 ± 0.21
SPAP (mmHg)	58.67 ± 7.28	60.55 ± 9.34	47.22 ± 5.6#†	55.85 ± 7.41†

E, peak early mitral inflow velocity; e', mitral valve ring myocardial diastolic early peak velocity; FAC, right ventricular fractional area change; LAEDD, left ventricle end diastolic diameter; LVEF, left ventricular ejection fraction; S', tricuspid annular peak systolic velocity; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.
* Compared with control group, p < 0.05. # Compared with control group, p < 0.0001. † Compared with baseline, p < 0.05.

Table 3. Clinical data after 24-h treatment and at 1-month follow-up

	Levosimendan (n = 30)	Control (n = 29)	p value
Clinical data after 24-h			
Urine discharge (ml)	1923 ± 285	1761 ± 256	0.026
Systolic BP (mmHg)	111.47 ± 24.13	118.03 ± 13.63	0.205
Diastolic BP (mmHg)	66.37 ± 14.59	70.83 ± 10.64	0.186
Heart rate (bpm)	69.03 ± 15.82	73.86 ± 10.67	0.176
SCr (μmol/L)	95.26 ± 26.68	103.56 ± 46.25	0.401
BNP (ng/ml)	957.95 (727.74, 1322.84)	1302.16 (1006.99, 1666.35)	0.005
1-month follow-up			
Death, n (%)	1 (3.3)	1 (3.4)	0.487
Hospitalization (days)	13.60 ± 3.97	11.52 ± 6.02	0.121
Readmission, n (%)	0 (0)	1 (3.4)	0.492

BNP, B-type natriuretic peptides; BP, blood pressure; SCr, serum creatinine.

diseases and the current guidelines. The rates of intravenous injections of diuretics, digitalis and nitrate are shown in Table 1, and no significant differences were found. Because patients with hypotension were excluded, dopamine and dibutylamine were not used in either group.

Levosimendan is a calcium-sensitizing agent that increases contractility in cardiomyocytes without increasing intracellular calcium concentrations and oxygen demand.[14,15] This makes levosimendan an optimal treatment strategy in a failing and hypoperfused ventricle. RV function may be improved through an increase in contractility in cardiomyocytes and improvements in left ventricular functions.

The normal right ventricle is a thin-walled and compliant structure that reacts poorly to pressure-overload. Levosimendan also dilates systemic and pulmonary blood vessels, possibly by opening adenosine triphosphate-dependent potassium channels.[16,17] Decreased systemic pulmonary artery pressure is associated with vasodilatation in the pulmonary vascular bed and improved left ventricle function, and it can also help levosimendan improve RV function.

Leather et al.[18] showed that levosimendan not only improved the contractility of the right ventricle but also decreased pulmonary pressure numerically better than dobutamine in accordance with the findings of Yilmaz et al.[7] Coddens et al.[19] showed that selective pulmonary arterial vascular smooth muscle relaxation was probably not the most important mechanism to explain the unloading and improvement in RV function with dobutamine. We also think that levosimendan improves ventriculovascular coupling of the right ventricle, along with the dual benefits of pulmonary vasodilatation and improved RV systolic function.

Parameters to assess diastolic function of the right ventricle are less well established compared to the left ventricle due to the irregular geometrical morphology of the right ventricle.[20] Currently, echocardiography, magnetic resonance imaging and single photon emission computed tomography myocardial imaging are used in clinical practice to evaluate RV function. Echocardiography is widely used because of its superiority in repeatability and convenience. In this study, we used S′, FAC and TAPSE as the parameters to evaluate RV function, and the SPAP was also calculated and compared between the two groups.

In patients with postcardiotomy low cardiac output syndrome, RV failure develops in approximately 25% of patients receiving left ventricular assist device support. However, recent studies have also suggested that left ventricular function may significantly affect RV function through ventricular interdependence. Experimental studies have indicated a very consistent RV response during left ventricular assist device support, including a decrease in RV afterload, increased compliance, and decreased contractility. In normal hearts, the net effect is an increase or no change in cardiac output. With a preexisting pathologic condition, the RV responses is qualitatively the same, however anatomic ventricular interaction is accentuated, leading to a greater decrease in RV contractility. The net effect is a decrease in cardiac output, which may require inotropic or RV mechanical support.[21] In this study, we found that levosimendan could improve left ventricular and RV functions and decrease pulmonary systolic pressure. The improvement in RV function may partly be due to the improvement in left ventricular function.

This study demonstrated the beneficial effects of levosimendan in the form of improved RV performance in a specific group of patients with significant ADHF. Limitations of the study include that it is a small scale study, and some of the patients were not given β-blockers or other drugs because of heart rate, blood pressure and onset of acute heart failure. Therefore, further adequately powered studies are required to determine whether these physiological observations can be applied to improve patient outcomes and assess the safety of this strategy.

CONCLUSIONS

In conclusion, levosimendan seems to provide more beneficial effects among patients with ADHF to improve RV function, along with a decrease in pulmonary pressure.

ACKNOWLEDGEMENTS

This study was supported by Science and Technol-

ogy Huimin Plan of Hebei province (No. 162777187).

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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