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ORIGINAL ARTICLE

Early Effect of Levosimendan in Systolic and Diastolic Parameters

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Abstract

Introduction: Heart failure (HF) is still one of the important causes of both mortality and recurrent hospitalization. Levosimendan is an important agent that reduces these outcomes in decompensated HF. We aimed to share the effects of levosimendan on various echocardiographic parameters and systolic and diastolic functions of the left ventricle in the early period.

Methods: Twenty patients with stage IV heart failure (ischemic or non-ischemic) according to NYHA, with resting blood pressure >100 mmHg, left ventricular ejection fraction <35%, and clinically unstable despite conventional therapy were included in the study. Before starting levosimendan, left and right ventricular systolic and diastolic functions and coronary flows were examined in echocardiography. The same echocardiographic parameters were re-examined in all patients 24 hours after levosimendan treatment.

Results: When we made the evaluations, it was observed that systolic functions improved in the early period after levosimendan, but it was observed that the improvement in diastolic functions did not occur in the early period.

Discussion and Conclusion: Since the echocardiographic evaluation was performed only 24 hours after levosimendan, it was considered necessary to re-examine the tests after 7 days, especially to evaluate the tests evaluating diastolic functions.

Keywords: AFI; Echocardiography; Heart failure; Levosimendan; Longitudinal strain.

Advanced heart failure (HF) is the condition that needs maximal medical therapy, surgery, or device use to prevent the progression of symptoms and signs. According to the New York Heart Association (NYHA) classification, recurrent hospitalizations and mortality are higher in patients with chronic HF who are class IIIb or IV. The prevalence of advanced HF is 5-10%[1].

While the results of the EURObservational Research Program Heart Failure Pilot Survey show that the one-year mortality is 7.2% in chronic HF, this rate rises to 75% in cases of advanced HF. This shows that one-year survival in advanced stage HF patients is much worse than many cancers[2]. In the acute decompensation of chronic heart failure, intravenous diuretics, nitrates, ACE inhibitors, ARBs, digitalis, and intravenous positive inotropic agents are used in the treatment. Levosimendan is thought to be a good choice in patients who cannot be compensated with these and who are not hypotensive[3]. Levosimendan sensitizes cardiac muscle to calcium without increasing cAMP and intracellular calcium concentration. It increases cardiac contraction. Studies show that levosimendan improves symptoms, reduces mortality, and reduces recurrent hospitalizations[4,5]. Therefore, levosimendan is frequently used in patients who cannot improve with standard treatment in decompensated heart failure.

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Materials and Methods

Twenty patients (50-90 years old) (5 women [25%], 15 men [75%]) with stage IV heart failure (ischemic or non-ischemic) according to NYHA, with resting blood pressure >100 mmHg, left ventricular ejection fraction <35%, and clinically unstable despite conventional therapy were included in the study. The study was applied to the patients with the regular routine consent form according to the Helsinki Declaration. The levosimendan treatment is used in the routine treatment. Only the parameters were included in the study.

The patients with acute coronary syndrome, acute heart failure, severe hypotension, advanced valve stenosis, atrial fibrillation, constrictive pericarditis, hypertrophic cardiomyopathy, benign or life-threatening tachycardia above 120/min, electrolyte problem, chronic obstructive pulmonary disease (COPD), uncontrolled diabetes, severe kidney failure, liver failure, and infections were not included in the study.

The compensated patients who later became decompensated were hospitalized at the coronary intensive care unit and the maximal conventional treatment was given. Diuretic therapy, IV nitrate, angiotensin-converting enzyme inhibitors (ACE) at the highest tolerated dose or angiotensin II receptor blocker, beta blockers and/or ivabradine, and digoxin were started as a maximal treatment in these patients. The patients with symptomatic relief after the maximal therapy were not included in the study.

Before starting levosimendan, left and right ventricular systolic and diastolic functions and coronary flows were examined in echocardiography. Afterwards, a loading dose of 12 mcg/kg/10 min followed by a maintenance dose of levosimendan at 0.1 mcg/kg/min was started in patients who could not achieve clinical partial relief in 24 hours with maximal treatment. The dose was decreased to half when hypotension developed. The same echocardiographic parameters were re-examined in all patients 24 hours after levosimendan treatment.

Transthoracic Echocardiography Parameters

All patients were examined with the General Electric Vivid E9 echocardiography device. M5S (1.5-4.5 MHz) was used as a probe. All images were recorded by the same person. All parameters were averaged three times in patients. Images were taken in the left lateral decubitus position. The same parameters were measured before and 24 hours after the administration of levosimendan from the same patient. For left ventricular systolic functions, Left Ventricular Ejection Fraction (LVEF) was calculated by means of LV diastolic and systolic volumes using the biplane Modified Simpson's method. LV longitudinal global strain value was found by using Speckle Tracking method and AFI software. For this, apical four-chamber, apical three-chamber, and two-chamber images were recorded from each patient. Event timing was performed from the aortic valve closure time and global longitudinal strain values were calculated for each patient with the automated function imaging (AFI) feature of the device. Left atrium (LA) anteroposterior diameter and LA volumes were compared.

Among patients with mitral regurgitation, dp/dt was measured in patients with mitral regurgitation flow velocity of 3 m/sec systolic velocity. Right ventricular longitudinal global strain value in right ventricle (RV) systolic function was calculated by Speckle Tracking from the apical-four chamber view. S wave was measured in the lateral annulus and septum with tissue Doppler. E and A wave, E/A ratio, DT (deceleration time) and IVRT (isovolumic relaxation time) as left ventricular diastolic function parameters, E/e' (which allows interpreting left ventricular filling pressure) value by looking at Em in the lateral annulus in tissue Dopplers were reached. Mitral flow propagation velocity was measured by imaging the diastolic filling pattern of the mitral valve with color Dopplers. LAD coronary flow was visualized and diastolic and systolic velocities and VTIs were recorded. Deceleration time of LAD diastolic flow was measured.

Statistical Method

Statistical analyses were performed using the PASW 18 program. All numerical values are given as mean±standard deviation. All non-numerical values were given as frequency and percentage. The Kolmogorov-Smirnov test was used to investigate the presence of normal distribution. Data obtained by sequential measurements (dependent data) were compared with the paired Student's t-test if they were normally distributed. Wilcoxon Signed Rank Test (non-parametric test) was applied to those who did not show normal distribution. Levene's Test for Equality of Variances in those with normal distribution in comparison of non-dependent data used. The Mann-Whitney U test was used for independent but not normally distributed subjects. A p value of less than 0.05 was considered significant.

Results

When the echocardiographic parameters obtained from our patients before the levosimendan infusion were compared with the values 24 hours after the infusion, EF (p=0.001), left ventricular global longitudinal strain

Table 1. Comparison of echocardiographic parameters and NYHA heart failure class before and after levosimendan

Echocardiographic parameters	Before levosimendan	48 hours after levosimendan	p
EF (%)	25.40±6.77	31.65±6.33	0.001
LV diastolic volume (ml)	183.50±57.76	166.30±56.51	0.004
LV systolicvolum (ml)	133.40±54.53	115.65±40.09	0.005
LV longitudinal strain (%)	-5.53±2.08	-6.41±1.89	0.002
RV longitudinal strain(%)	-10.6±5.16	11.9±3.37	0.147
dp/dt (mmHg/sec) of mitral regurgitation flow	589.62±133.14	883.25±310.39	0.008
Lateral S (m/sn)	0.041±0.014	0.046±0.017	0.086
Septal S (m/sn)	0.033±0.011	0.044±0.016	0.047
LA volume (ml)	82.80±40.44	80.20±30.03	0.955
LA diameter /cm)	4.85±0.55	4.94±0.57	0.586
E/e'	20.77±13.54	14.87±13.95	0.040
E/A	2.51±1.15	1.89±1.09	0.021
DT (msn)	177±78.93	174.50±67.75	0.828
IVRT(msn)	84±35.75	84.20±34.75	0.977
Mitral inflow flow propagation velocity (cm/sec)	34.75±11.54	35.70±9.39	0.753
LAD VTI diastolic coronary flow velocity time integral (cm/sn)	9.68±6.63	10.19±6.03	0.629
LAD peak systolic flow VTI (cm/sec)	3.21±1.88	3.72±2.12	0.519
LAD diastolic flow deceleration time (ms)	765.85±444.26	785.50±370.81	0.575
LAD dVTI/sVTI	3±1.48	2.87±1.03	0.707
NYHA Class	4±0	2.40±0.50	0.001

EF: Ejection fraction; LV: Left ventricle; RV: Right ventricle; dp/dt: The rate of pressure change (dP) with time (dt) during isovolemic contraction of the cardiac ventricles; LA: Left atrium; DT: Deceleration time; IVRT: Isovolumic relaxation time; LAD: Left anterior descending artery; VTI: Velocity time integral; NYHA: New York Heart Association.

(p=0.002), and Dp/dt increase (p=0.008) were found statistically significant (Table 1). The amount of decrease in left ventricular diastolic volume (p=0.004) and systolic volumes (p=0.005) was found to be significant. An increase in the septal S wave (p=0.047) and a significant decrease in the E/E' level (p=0.040) were observed in the images taken on tissue Doppler, and it was thought that there was a significant decrease in LA pressure and PCW due to the left ventricular end diastolic pressure. A significant (p=0.001) regression was observed in the NYHA heart failure class. When we divided the groups in the study into those with and without ischemic heart disease, no significant difference was observed between the parameters examined. In addition, no significant difference was observed between the parameters.

Parameters Found to be Insignificant

An increase in right ventricular longitudinal strain, a decrease in LA diameter, and a decrease in LA volume were found to be insignificant. In diastolic function evaluations, changes in DT and IVRT, and an increase in flow propagation velocity of mitral valve inflow were found to be insignificant. In the evaluation of coronary flow, the increase in the VTI of the diastolic flow in the LAD flow, the increase in the LAD flow systolic VTI, and the increase in the deceleration time of the LAD diastolic flow were found to be statistically insignificant.

Discussion

In acute decompensation of chronic heart failure, in cases unresponsive to standard treatment, the use of levosimendan increases the sensitivity of myocardial contractile proteins to calcium and reduces symptoms with positive inotropic and vasodilator effects (inodilator effect) by providing peripheral vascular dilation with ATP-sensitive K channel activation.

It has been shown to shorten the duration of hospitalization and reduce recurrent hospitalizations[6]. In our study, the patients were interned as class IV according to NYHA and regressed to a clinically significant lower class after levosimendan. The effects of levosimendan on echocardiographic parameters were examined in various studies[7].

In a study by McLean AS et al.[8], EF increase with levosimendan was found on the first day, RV strain increase,

LA volume decrease, and E/e' decrease on the 7th day. Similarly, in our study, an increase in EF before and after levosimendan was found to be significant. Decreases in left ventricular diastolic and systolic volumes were found to be significant. Left ventricular global longitudinal strain values were significantly increased. Although in the same study E/e' was mostly decreased on the 7th day, in our study, it was significant on the first day. In addition, while the E/A ratio was 2.5±1.5 at the beginning, that is, the restrictive pattern was present, it was 1.89±1.09 after levosimendan and the restrictive pattern was significantly decreased (p=0.021).

Another difference in our study is that the LA volume decreased and there was no significant increase in the RV strain value; changes in these values reached a significant level on the 7th day in the mentioned study. Our study supports that these values do not change at an early level.

In our study, left ventricular longitudinal strain values were measured with the AFI (automated function imaging) method, and strain measurement with this method has not been encountered before in the literature in those receiving levosimendan treatment. In similar strain studies, strain averages were taken with the speckle tracking method and calculated without using this method[9]. In our study, left ventricular global longitudinal strain values were found with AFI and increased significantly with levosimendan. In this respect, it was thought that AFI could be an accurate and easy-to-use method in calculating left ventricular global longitudinal strain.

Kasikcioglu et al.[10] detected an increase in the lateral wall S wave with levosimendan by tissue Doppler. In our study, the S wave change in the lateral wall was found to be insignificant, while the increase in the S wave in the septal wall was significant. The reason for this may be that the S velocity of the lateral wall may be more impaired in patients with excessive lateral wall hypokinesia due to ischemic heart disease, and although the increase in global left ventricular functions with levosimendan increased significantly, it may not have increased in the lateral wall contractile function. For this reason, it was thought that a common evaluation could be recommended not only by looking at the lateral or only septal S wave parameters, but also by the tissue Doppler evaluations. It was considered more important to evaluate the parameters. Parissis et al.[11] found that the mitral flow propagation velocity increased in 24 hours with levosimendan.

In our study, there was an increase in mitral flow propagation velocity, but it was not found significant. There was no significant change in diastolic function parameters such as DT and IVRT. This was thought to be because, as McLean AS et al.[8] found in their study, a longer time was required for diastolic parameters to recover. The reductions in E/A ratio and E/e' ratios obtained from mitral valve inflow were found to be statistically significant. It was thought that these two parameters decreased in the early period related to the decrease in left ventricular end-diastolic pressure.

In the study by Ikonomidis et al.[12], LAD coronary flow diastolic velocity, diastolic flow VTI, diastolic VTI/systolic VTI, and LAD diastolic flow DT were measured with levosimendan and it was observed that all of them increased significantly. However, we did not find the increase in these values statistically significant, which was interpreted as the inclusion of ischemic heart patients in our study.

Conclusion

It has been concluded that AFI is an easy and reliable method to calculate left ventricular spherical longitudinal strain and that the evaluation of global left ventricular systolic functions is more meaningful than tests that evaluate regional mobility such as tissue Doppler. Tests to evaluate left ventricular diastolic functions with levosimendan do not provide a complete evaluation when performed in the early period. We can see more significant differences as late as one week. In the AFI method, since the program was written for left ventricular strain calculation, it was also thought that it did not give accurate results due to the difference in right ventricular anatomy.

As the limits of our study, levosimendan was not compared with placebo. Since the echocardiographic evaluation was performed only 24 hours after levosimendan, it was considered necessary to re-examine the tests after 7 days, especially to evaluate the tests evaluating diastolic functions.

In the early phase, it is stated that levosimendan improved diastolic dysfunctions like systolic dysfunctions in some of the studies. In our study, we detected the reverse. By this study, we stated that the evaluation of diastolic functions might be done in a late phase after levosimendan treatment. We also stated that global longitudinal strain evaluation is much more efficient than tissue Doppler assessment for left ventricular systolic functions evaluation.

Ethics Committee Approval: Not available because the study was applied to the patients with the regular routine consent form according to the Helsinki Declaration. The levosimendan treatment is used in the routine treatment. Only the parameters were included in the study.

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