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Assessment of sustained effects of levosimendan and dobutamine on left ventricular systolic functions by using novel tissue Doppler derived indices in patients with advanced heart failure

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Abstract

Background: *Previous studies comparing levosimendan vs. dobutamine have revealed that levosimendan is better in relieving symptoms. Echocardiographic studies have been done using second measurements immediately following a dobutamine infusion or while it was still being administered. The aim of our study was assessment of sustained effects of 24 h levosimendan and dobutamine infusions on left ventricular systolic functions.*

Methods: *A total of 61 patients with acutely decompensated heart failure with New York Heart Association (NYHA) class III or IV symptoms were randomized to receive either levosimendan or dobutamine 2:1 in an open label fashion. Before and 5 days after the initiation of infusions, functional class was assessed, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) levels and left ventricular ejection fraction (LVEF), mitral inflow peak E and A wave velocity, and E/A ratios were measured; using tissue Doppler imaging, isovolumic myocardial acceleration (IVA), peak myocardial velocity during isovolumic contraction (IVV), peak systolic velocity during ejection period (Sa), early (E') and late (A') diastolic velocities, and E'/A' and E/E' ratios were measured.*

Results: *The NYHA class improved in both groups, but improvements were prominent in the levosimendan group. NT-proBNP levels were significantly reduced in the levosimendan group. Improvements in LVEF and diastolic indices were significant in the levosimendan group. Tissue Doppler-derived systolic indices of IVV and IVA increased significantly in the levosimendan group.*

Conclusions: *Improvements in left ventricular systolic and diastolic functions continue after a levosimendan infusion.* (Cardiol J 2015; 22, 1: 87–93)

Key words: levosimendan, dobutamine, acute heart failure, isovolumic acceleration

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Introduction

Heart failure (HF) patients are generally treated with diuretics, vasodilators, and beta-blockers in the long term. Positive intravenous inotropes are considered for therapy when the exacerbation of HF is accompanied by evidence of low cardiac output, such as hypotension and oliguria; however, their long-term usage is limited due to the high rate of mortality [1].

Levosimendan is a positive inotropic drug with a vasodilator effect. It exerts positive inotropic effects by binding cardiac troponin C and sensitizing cardiac myofilaments to calcium without increasing intracellular calcium concentrations [2]. The active metabolite of levosimendan peaks approximately 3 days after the start of drug infusion and has a half-life of approximately 80 h; thus the drug's action is expected to last for 2 weeks [3]. Dobutamine has a serum half-life of 2 min and has no known active metabolite [4].

Isovolumic acceleration (IVA) is a novel tissue Doppler parameter for the assessment of systolic functions of both left and right ventricles [5, 6]. IVA reflects the acceleration of the myocardium at the very beginning of the isovolumic contraction velocity (IVV) period. IVA remains unaffected by the changes in the preload and afterload within the physiological range [5, 7]. It can detect even small changes in contractile function and is well correlated with the invasive or noninvasive measures of left ventricle (LV) dp/dt [5, 8].

In the present study, we aimed to determine whether levosimendan and dobutamine infusions have any ongoing effects on LV systolic and diastolic functions using conventional echocardiographic and tissue Doppler imaging (TDI)-derived parameters after the completion of infusions in acute decompensated HF patients.

Methods

Study design and patient population

Seventy-five consecutive patients in sinus rhythm with severe LV systolic dysfunction (ejection fraction [EF] < 35%) who had been hospitalized due to acutely decompensated HF with New York Heart Association (NYHA) class III or IV symptoms despite medical therapy (including diuretics, ACE inhibitors/ARBs, beta-blockers, and spironolactone) were decided to be administered inotropic therapy and evaluated. The exclusion criteria were: patients who were younger than 18 years or older than 80 years, in cardiogenic shock, had supine systolic blood pressure < 85 mm Hg, heart rate > 135 bpm, serious arrhythmias, hepatic or renal impairment (creatinine > 5 mg/dL), HF due to restrictive or hypertrophic cardiomyopathy, severe valvular disease except functional mitral regurgitation, chronic obstructive pulmonary disease, a levosimendan infusion within 6 months, recent myocardial infarction (< 2 months) or acute coronary syndromes, acute or chronic infectious or inflammatory disease, or poor echocardiographic image quality. The study protocol was approved by the institutional Ethics Committee, and written informed consent was obtained before randomization.

Five patients with poor echocardiographic image quality received inotropic infusions but were not included in the study. Patients were randomized to receive either levosimendan (n = 47) or dobutamine (n = 23) 2:1 in an open label fashion. Levosimendan was administered for 24 h, and a 12 mg/kg/min loading dose was given for 10 min to 22 patients whose systolic blood pressure was > 90 mm Hg. All patients received a continuous infusion of 0.1 mg/kg/min administered for 50 min and up titrated to an infusion rate of 0.2 mg/kg/min if tolerated. Dobutamine was infused for 24 h at an initial dose of 5 mg/kg/min; up titration of the dobutamine dose was left for the physician to decide. Atrial fibrillation occurred in 1 patient in the levosimendan group; 6 patients in the levosimendan group and 2 patients in the dobutamine group whose functional class was improved refused to stay in hospital for 5 days or come to hospital again on the 5th day for echocardiographic measurements and thus were discharged and not included in the study. A total of 61 patients data who received levosimendan (n = 40) or dobutamine (n = 21) were analyzed (Fig. 1).

Conventional echocardiographic examination

Echocardiographic examinations were conducted before drug administration and 5 days after the initiation of treatment. All of the transthoracic echocardiographic examinations were performed using the GE vivid S6 Vingmed system 5 (Norway, Horten) equipped with 2.5–4 MHz transducers. All of the patients were examined in the left lateral and supine positions with 2-dimensional, M-mode, pulsed, and color flow Doppler echocardiography. A single lead electrocardiogram was recorded continuously. An average of at least 5 cardiac cycles were obtained for all measurements. Echocardiographic analyses were performed by an experienced echocardiography specialist who was blinded to all data.

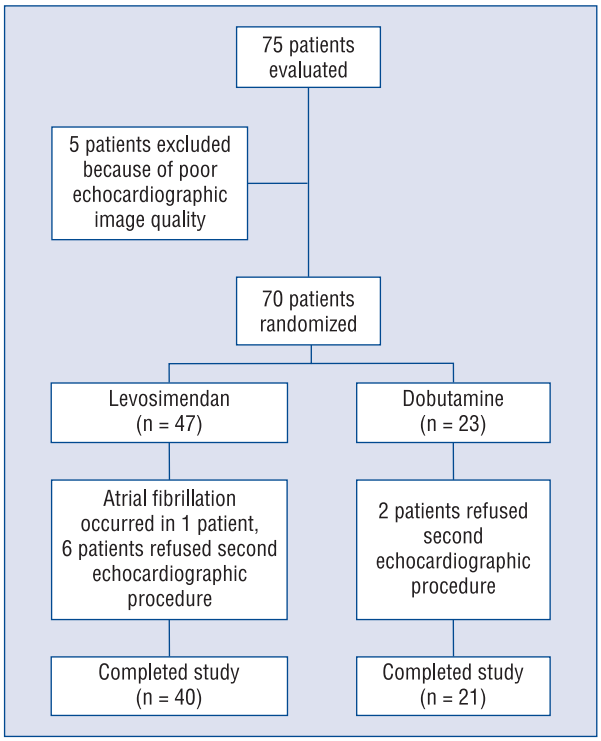

Figure 1. Patient disposition.

M-mode measurements and conventional Doppler echocardiographic examinations were performed based on the criteria of the American Society of Echocardiography and European Society of Echocardiography guidelines [9]. Left atrial, LV end-systolic, and end-diastolic dimensions were measured in the parasternal long-axis views. LVEF was estimated by the Simpson's rule. The mitral inflow peak velocity during early filling (E) and late filling from atrial contraction (A) as well as the E/A ratio were measured.

Tissue Doppler imaging

Doppler tissue echocardiography was performed using transducer frequencies between 3.5 to 4.0 MHz, by adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15––20 cm/s was reached, and using the minimal optimal gain. Five consecutive cycles were recorded with a frame rate greater than 150 fps. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. Every effort was made to align the pulsed wave cursor so that the Doppler angle of incidence was as close to 0 as possible to the direction of these walls. In the apical 4-chamber view, the pulsed Doppler sample volume was subsequently placed at the level of LV lateral and septal basal wall at end-expiration [10].

Peak myocardial IVV, peak myocardial systolic velocity (Sm), peak early and late diastolic velocities (E' and A'), and IVA time were measured. Myocardial acceleration during IVA was defined as the ratio of IVV divided by the acceleration time. For intraobserver variability of the Sm, IVV and IVA obtained from 10 random patients measured repeatedly within intervals of a few minutes. Intraobserver variability of Sm, IVV, and IVA was found to be $r = 0.98$, $r = 0.97$ and $r = 0.97$, respectively.

Blood samples for analyses of natriuretic peptide levels were drawn from patients in the supine position before the echocardiographic examinations (baseline and after 5 days) using Elecsys N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) kits (Roche diagnostics, Mannheim, Germany) by an observer who was blinded to patient identity and treatments.

Statistical analysis

Statistical analyses were performed using the SPSS software version 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine the normal distribution. Descriptive analyses are presented using means and standard deviations or median and the interquartile range (range from the 25^{th} to the 75^{th} percentile). The categorical variables are expressed as numbers and percentages. Numerical variables were compared using the Mann-Whitney U or Student's t-test. Categorical data were compared with the χ^2 test. The paired Student's t-test or Wilcoxon test were used to compare the measurements at two time points. Intraobserver agreement was assessed with Spearman's correlation coefficients, and a p value < 0.05 was considered significant.

Results

Patients randomized to either the levosimendan or dobutamine group were similar with respect to pretreatment characteristics and concomitant medications (Table 1). As indicated in Table 2, the levosimendan group was associated with a significant reduction in NT-proBNP levels and a significant improvement in the NYHA class. In the dobutamine group, the NYHA class significantly improved, but the reduction in NT-proBNP levels was not significant. The improvement in the NYHA class was more prominent in the

Table 1. Baseline characteristics of the patients according to treatment group.

Variable	Levosimendan (n = 40)	Dobutamine (n = 21)	P
Age [years]	59.7 ± 11.2	63.8 ± 9.0	0.151
Gender, men	32 (80%)	18 (85.7%)	0.430
Body mass index [kg/m^2]	27.9 ± 4.6	27.6 ± 5.8	0.864
NT-proBNP [pg/mL]	7099 (2754–12100)	4130 (2168–9060)	0.333
Creatinine [mg/dL]	1.2 (1.0–1.4)	1.3 (1.1–1.8)	0.289
Systolic blood pressure [mm Hg]	116.5 ± 22.9	115.4 ± 23.0	0.863
Diastolic blood pressure [mm Hg]	68.0 ± 12.3	65.2 ± 12.0	0.395
Heart rate [bpm]	77 (66–83)	75 (66–82)	0.790
Hypertension	21 (52.5%)	9 (42.9%)	0.474
Diabetes mellitus	23 (57.5%)	11 (52.4%)	0.702
Hyperlipidemia	14 (35%)	6 (28.6%)	0.611
Heart failure etiology, ischemic	32 (80%)	17 (81%)	0.606
NYHA class IV	25 (62.5%)	15 (71.4%)	0.486
Left ventricular ejection fraction [%]	24.5 ± 5.4	25.7 ± 5.6	0.412
Medication:			
ACEI	29 (72.5%)	15 (71.4%)	0.286
Angiotensin II blockers	5 (12.5%)	2 (9.5%)	0.544
Beta-blockers	34 (85%)	17 (81%)	0.473
Diuretic	40 (100%)	21 (100%)	
Spironolactone	25 (62.5%)	13 (61.9%)	0.964
Statin	7 (17.5%)	4 (19%)	0.570
Aspirin	30 (75%)	15 (71.4%)	0.763
Clopidogrel	8 (20%)	7 (33.3%)	0.251
Nitrate	13 (32.5%)	6 (28.6%)	0.753

Values are presented as mean ± standard deviation, median (interquartile range) or number or percentage of patients; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide; NYHA — New York Heart Association; ACEI — angiotensin-converting enzyme inhibitors

Table 2. Clinical and laboratory parameters before and after treatment in the levosimendan and dobutamine groups.

Variable	Levosimendan		P	Dobutamine		P
	Before	After		Before	After	
SBP [mm Hg]	116.5 ± 22.9	110.1 ± 17.6	0.057	115.4 ± 23.0	110.4 ± 14.9	0.325
DBP [mm Hg]	68.0 ± 12.3	65.5 ± 11.6	0.207	65.2 ± 12.0	65.1 ± 11.3	0.971
Heart rate [bpm]	77 (66–83)	77 (67–83)	0.675	75 (66–82)	77 (69–82)	0.955
Creatinine [mg/dL]	1.2 (1.0–1.4)	1.3 (1.0–1.5)	0.992	1.3 (1.1–1.8)	1.5 (1.1–1.8)	0.582
NT-proBNP [pg/mL]	7099 (2754–12100)	3484 (2020–5647)	< 0.001	4130 (2168–9060)	3830 (1768–18653)	0.594
NYHA class	3.6 ± 0.5	2.2 ± 0.7	< 0.001	3.7 ± 0.5	3.1 ± 0.7	0.003
Hematocrit [%]	37.7 ± 5.0	37.0 ± 5.7	0.200	36.8 ± 5.9	35.0 ± 5.1	0.081

Values are presented as mean ± standard deviation or median (interquartile range); SBP — systolic blood pressure; DBP — diastolic blood pressure; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide; NYHA — New York Heart Association

levosimendan group ($p < 0.001$ vs. $p = 0.003$). Systolic and diastolic blood pressures, heartbeat, creatinine levels, and hematocrit percentages did not significantly change in the levosimendan and dobutamine groups.

Conventional echocardiographic findings

In the group treated with levosimendan, LV systolic and diastolic diameters and left atrial diameter significantly reduced and LVEF significantly improved (Table 3). In the dobutamine group, none

Table 3. Echocardiographic parameters before and after treatment in the levosimendan and dobutamine groups.

Variable	Levosimendan		P	Dobutamine		P
	Before	After		Before	After	
Two-dimensional, M-mode, PW Doppler measurements						
LVEDd [cm]	6.4 ± 0.8	6.3 ± 0.8	< 0.001	6.3 ± 0.7	6.3 ± 0.8	0.896
LVESd [cm]	5.5 ± 0.8	5.3 ± 0.9	0.003	5.3 ± 0.7	5.3 ± 0.8	0.613
IVS [cm]	0.99 ± 0.18	1.00 ± 0.15	0.501	0.98 ± 0.2	0.96 ± 0.18	0.408
PW [cm]	0.97 ± 0.16	0.97 ± 0.14	0.711	0.94 ± 0.2	0.93 ± 0.23	0.607
LVEF [%]	24.8 ± 5.4	30.2 ± 4.5	< 0.001	26.1 ± 5.5	27.4 ± 5.2	0.107
LA diameter [cm]	4.7 ± 0.5	4.6 ± 0.5	0.004	4.9 ± 0.7	4.8 ± 0.5	0.363
E [cm/s]	95.9 ± 27.7	88.8 ± 23.6	< 0.001	98.7 ± 24.0	97.5 ± 22.7	0.008
A [cm/s]	42.1 ± 15.0	44.4 ± 15.2	< 0.001	39.6 ± 11.2	39.8 ± 11.8	0.168
DT [ms]	150.9 ± 36.4	155.4 ± 37.5	< 0.001	142.8 ± 27.2	142.2 ± 27.5	0.624
E/A	2.5 ± 1.0	2.2 ± 0.8	< 0.001	2.6 ± 0.7	2.5 ± 0.7	0.013
Tissue Doppler						
E′ [cm/s]	5.1 ± 1.5	6.0 ± 1.8	< 0.001	5.01 ± 1.3	5.2 ± 1.3	0.031
A′ [cm/s]	3.8 ± 1.1	4.6 ± 1.6	< 0.001	4.1 ± 0.9	4.2 ± 0.9	0.083
E′/A′	1.5 ± 0.7	1.4 ± 0.6	0.580	1.3 ± 0.3	1.3 ± 0.4	0.223
E/E′	20.6 ± 9.3	14.9 ± 5.2	< 0.001	20.8 ± 7.0	20.1 ± 6.9	0.006
Sa [cm/s]	4.0 ± 0.9	4.6 ± 1.0	< 0.001	4.1 ± 0.08	4.2 ± 0.7	0.264
IVV [cm/s]	3.6 ± 0.7	4.2 ± 0.8	< 0.001	3.7 ± 0.9	3.8 ± 0.8	0.100
IVA (m/s^2)	1.1 ± 0.2	1.4 ± 0.3	< 0.001	1.1 ± 0.4	1.2 ± 0.4	0.088

Values are presented as mean ± standard deviation; LVEDd — left ventricular end-diastolic diameter; LVESd — left ventricular end-systolic diameter; IVS — interventricular septum; PW — posterior wall; LVEF — left ventricular ejection fraction; LA — left atrium; DT — deceleration time; E — mitral inflow peak early diastolic wave velocity; A — mitral inflow peak late diastolic wave velocity E′ — flow velocity of the early diastole using tissue Doppler echocardiography; A′ — flow velocity of the late diastole using tissue Doppler echocardiography; Sa — peak velocity of myocardial systolic wave; IVV — isovolumic velocity; IVA — isovolumic acceleration

of these parameters changed significantly. The mitral E velocity and E/A ratio significantly increased, and the mitral A velocity and deceleration time significantly increased in levosimendan-treated patients, but none of these parameters significantly changed in dobutamine-treated patients (Table 3).

Tissue Doppler findings

In the levosimendan group, E', A', Sa, IVV, and IVA parameters significantly increased, E/E' significantly decreased, and the decrease in E'/A' was not significant. None of these parameters changed significantly in the dobutamine group (Table 3).

Discussion

The present study indicates that a 24-h infusion of levosimendan is better than dobutamine in terms of improving LV systolic and diastolic functions based on both conventional echocardiography parameters and TDI-derived parameters as well as decreasing NT-proBNP levels 5 days after the initiation of treatment.

Levosimendan has a half-life of approximately 1 h [11], but levosimendan's active metabolites are expected to sustain its effects up to 2 weeks [3]. Dobutamine has a short half-life and has no known active metabolite [4], but it has been suggested that after short-term infusion, the benefit can last for 30 days or more; this phenomenon is called the "dobutamine holiday" [12]. The persistence of clinical benefits after dobutamine infusion has been attributed to sustained improvement in myocardial contractility [12], a training-like effect on skeletal muscles [13], and an improvement in vascular endothelial function [14].

Studies comparing levosimendan and dobutamine using echocardiographic parameters generally performed a second echocardiographic examination just after inotrope infusions [15–17]. We performed echocardiographic measurements 5 days after the initiation of infusions to determine whether the favorable effects of the levosimendan and dobutamine continue following infusions.

Levosimendan exerts its positive inotropic effect without impairing diastolic relaxation [18],

whereas dobutamine increases myocardial cyclic adenosine monophosphate (cAMP) by stimulating the beta-adrenoreceptors. Raised cAMP concentrations causes intracellular calcium to increase, which exacerbates diastolic dysfunction [1]. Parissis et al. [19] showed that levosimendan infusion improved echocardiographic markers of abnormal LV diastolic function. Consistent with this study, in our study a levosimendan infusion lead to a significant increase in mitral A wave and deceleration time and a significant decrease in E/A and E/E' ratios. Dobutamine infusion did not cause any significant change in diastolic function parameters.

In a study comparing the effect of levosimendan and dobutamine infusion on left atrial functions [20], levosimendan infusions improved diastolic functions, decreased the E wave and E/A and E/E' ratios and increased the A wave significantly. Dobutamine infusions improved only the E/E' ratio. Duman et al. [21] also showed improvements in diastolic functions with levosimendan infusions, significant decreases in E/A and E/E' ratios and an increase in the A wave, deceleration time, and isovolumic relaxation time. Dobutamine infusions did not cause any significant change.

Both levosimendan and dobutamine enhance LV systolic function. In studies comparing levosimendan and dobutamine, some showed significant improvement in LVEF [15, 20, 21] both with levosimendan and dobutamine, but in a study in which patients were treated with carvedilol [17], the dobutamine group did not show an improvement in LVEF. In our study, LVEF significantly improved in the levosimendan group, but not in the dobutamine group. We think there are two possible reasons for this finding. In our study, 81% of patients in the dobutamine group were on beta-blocker therapy, and this might attenuate effects of dobutamine. The second possible explanation is that we evaluated echocardiographic parameters 5 days after initiation of infusions, thus dobutamine's effects culminated and dobutamine did not have sustaining effects.

LVEF and Sm are indicators of systolic function, but they are affected by loading conditions. Decompensated HF patients commonly take a considerable amount of diuretics. The loading conditions of these patients are unstable. IVA is a novel tissue Doppler parameter. IVA remains unaffected by preload and afterload changes within the physiological range [5, 7]. It can detect even small changes in the contractile function and is well correlated with the invasive or noninvasive measures of LV dp/dt [5, 8]. This parameter has been successfully validated in clinical studies [22–24]. Improvements in IVA were significant for the levosimendan group but not the dobutamine group in our study. The effects of dobutamine seem to culminate directly following an infusion. Dobutamine also caused improvements in the NYHA class, but the prominent improvements in the NYHA class with levosimendan infusions can be explained by the ongoing effects of active metabolites.

In the SURVIVE trial [25], BNP levels markedly decreased at day 1, both with levosimendan and dobutamine. After day 1, the BNP level remained low with levosimendan but rapidly increased with dobutamine and nearly returned baseline levels at day 5 in the SURVIVE trial. These results are consistent with our study; the NT-proBNP reduction was significant in the levosimendan group but not in the dobutamine group. This can also be explained by the lack of extended effects of dobutamine.

Limitations of the study

The major limitation is the small size of our patient groups. Additionally, systolic function parameters were not compared with the parameters obtained from cardiac catheterization. New imaging modalities to evaluate LV systolic and diastolic functions such as cardiac magnetic resonance imaging and speckle tracking echocardiography were not used in our study.

Conclusions

Improvements in functional capacity and LV systolic and diastolic functions continue after levosimendan infusions but not after dobutamine infusions, as expressed by conventional echocardiographic and TDI-derived parameters in patients with acute decompensated HF.

Conflict of interest: None declared

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