Received: 13 December 2017 | Revised: 5 May 2018 | Accepted: 21 June 2018

DOI: 10.1002/jcu.22627

WILEY

RESEARCH ARTICLE

Short-term effects of levosimendan on strain/strain rate markers in patients with nonischemic dilated cardiomyopathy

Tuncay Kırış MD[1] | **Eyüp Avcı MD**[2]

[1]Department of Cardiology, Izmir Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey

[2]Cardiology Department, Balikesir University Faculty of Medicine, Balikesir, Turkey

Correspondence
Tuncay Kiris, Atatürk Eğitim Araştırma Hastanesi, Basın Sitesi 35360, Izmir, Turkey.
Email: drtkiris@hotmail.com

Abstract

Objective: To investigate whether repetitive measurements of speckle tracking echocardiography (STE)-derived strain (S) and strain rate (SR) could reveal changes in left ventricular function in patients with nonischemic dilated cardiomyopathy treated with levosimendan.

Methods: We included 22 consecutive patients (age 53 ±12 years) with an ejection fraction (EF) below 35% and New York Heart Association (NYHA) class III-IV symptoms that required intravenous inotropic support despite optimal medical therapy. The absence of any occlusive coronary artery disease was identified via previous coronary angiography in all patients. Echocardiographic variables, including strain/strain rate, and NYHA functional class, were evaluated before and after levosimendan infusion at the 72nd hour and one month.

Results: The strain and strain rate values for both left and right ventricles were observed to be increased NYHA functional class and left ventricular EF (P <.05).

Conclusion: STE can successfully completed conventional echocardiography in the evaluation of patients with decompensated heart failure who were treated with levosimendan.

KEYWORDS

levosimendan, nonischemic cardiomyopathy, strain/strain rate

1 | INTRODUCTION

Heart failure (HF) remains a serious public health problem with increasing incidence, a poor prognosis, and a frequent need for rehospitalization.[1,2] Levosimendan increases myocardial contractility by stabilizing the calcium-bound conformation of troponin C via its high affinity to bind to the N-terminal lobe of this regulatory protein.[3,4] As an additional effect, levosimendan opens the K-ATP dependent channels on cytosolic and mitochondrial membranes, increases the K+ concentration in the mitochondrial cytosol, and thus may delay apoptosis of myocytes in HF patients with heart failure.[5,6] The pharmacokinetics of levosimendan are linear and the its plasma concentration of the drug increases in a dose-proportional manner after single dose intravenous administration and infusion of the drug.[7,8] Data from noninvasive studies has shown that the maximal hemodynamic response to levosimendan is occurs 24-48 hours after stopping the end of infusion. This prolonged hemodynamic action of levosimendan is a result of the formation of active metabolites.[9,10] Data regarding the effects of levosimendan on left ventricular (LV) systolic and diastolic function in patients with advanced HF is limited. The literature includes reports that used conventional echocardiographic measurements to demonstrate the improvements in systolic and diastolic function of both ventricles.[11–14] However, development of more sophisticated imaging techniques enables further evaluation of myocardial contractility and relaxation and, hence, further evaluation of the drug effects on myocardial function. Speckle tracking echocardiography (STE) is a promising imaging modality that enables further evaluation to assess myocardial contractility beyond the ejection fraction (EF) measurement, which only provides information about myocardial pump function. Strain and strain rate measurements can demonstrate deterioration of myocardial tissue before a reduction in the EF appears.[15] Global longitudinal strain (S) and strain rate (SR) by STE provided both objective, quantitative and validated measurements of LV function.[16,17] The serial measurements of these parameters variables were shown to be provide reliable and sensitive indices for changes in LV systolic function during levosimendan treatment in ST-elevation myocardial infarction patients developing acute HF.[18] In a previous study, Parissi et al. assessed levosimendan effects on myocardial parameters,

including cardiac volume, cardiac wall tension, and LVEF, the first month after its administration. They found an increase in LVEF and a recovery in cardiac performance after levosimendan infusion.[19] In addition, it has been shown that the maximal hemodynamic response to levosimendan is seen for 24-48 hours after stopping the infusion. Therefore, we chose the 72nd hour and one month as the time points at which to measure the effects of levosimendan. The aim of our study was to investigate whether repetitive measurements of STE-derived S and SR were indicative of changes in LV function in patients with nonischemic dilated cardiomyopathy who were treated with levosimendan.

2 | METHODS

2.1 | Study population and design

In this study, we included 22 consecutive patients with acute decompensated HF (age 53 ±12 years; 13 males, 9 females), acute or gradual exacerbation of resting HF signs and symptoms, requiring additional immediate therapy and intravenous inotropic support despite optimal medical therapy, with an EF below 35% and who were severely symptomatic (New York Heart Association ([NYHA)]-III/IV) symptoms. All patients received levosimendan with a loading dose of 24 μg/kg/min for 10 minutes followed by an infusion of 0.1 μg/kg/min for 24 hours. All patients were followed in the coronary intensive care unit under continuous ECG monitoring and frequent blood pressure measurements. In patients with systolic blood pressure (SBP) < 90 mm Hg, a loading dose was avoided. Hypotension (SBP <90 mm Hg), dizziness, or headache, were indicators for a dose reduction to 0.025-0.05 μg/kg/min. The infusion was interrupted if sustained ventricular tachycardia and/or severe hypotension (SBP < 80 mm Hg) occurred. Strain, strain rate, EF and functional capacity of all patients were assessed and recorded before and after the levosimendan infusion at the 72nd hour and one month. No change was applied in any of the other treatment protocols. Patients with atrial fibrillation, coronary artery disease, heart valve disease, obstructive hypertrophic cardiomyopathy, myocarditis, second or third degree atrioventricular block, severe chronic obstructive pulmonary disease, hepatic dysfunction (liver enzymes two times higher than normal), serum creatinine levels higher than 2.5 mg/dL, hypokalemia, hyperkalemia, or chronic inflammatory disease, were excluded from the study. Absence of occlusive coronary artery disease had been identified via previous coronary angiography in all patients. Written informed consent was obtained from all of the participants. The study protocol was approved by the local ethics committee and was conducted in accordance with the declaration of Helsinki.

2.2 | Transthoracic echocardiography measurements

Echocardiographic examination was performed by an experienced physician without prior knowledge of the patient's clinical data, using a standard sonographic system (Vivid 7, digital GE-Vingmed Ultrasound, Horten, Norway) equipped with a 2.5 MHz-6 MHz phased array sector probe. Left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) were obtained from the parasternal long axis view according to the American Society of Echocardiography recommendations.[16] The left ventricular EF was measured in apical four and two chamber views using the Simpson method. Mitral E and A velocities were obtained by placing the sample volume of the pulsed wave Doppler at the mitral leaflet tips in an apical four chamber view. Mitral annular Ea, and Aa velocities were measured by pulsed tissue Doppler from the lateral mitral annulus. All of these variables were obtained during 3 consequent sinus beats, and the mean values were calculated. The right ventricular systolic function was measured by using tricuspid annular plane systolic excursion (TAPSE), measured by M-mode echocardiography at the junction of the tricuspid valve and right ventricular free wall in the apical four chamber view. The strain rate mode was used in apical four and two chamber views. The gain, filter, and pulse repetition frequency were adjusted to optimize the color saturation and for the highest possible frame speed. The width and depth of the scanned sector were optimized (so that the minimum width of the sector in each axis was large enough to allow visualization of the LV walls). For our study, the lowest acceptable frame speed was 90 frames per second (giving a temporal resolution less than 11 milliseconds). The Nyquist "strain rate" limit was adjusted as ± 4 seconds^{-1} and the strain length was adjusted to 12 mm. At least 3 consequent beats were taken into the memory of the echocardiography device and were analyzed offline by the internal software (EchoPac 6.3.6, GE-Vingmed). The strain rate and strain curves of 3 longitudinal plans of the basal and mid segments of the opposite walls were shown at the same time. Two different observers investigated the strain and strain rate in 5 randomly selected records to evaluate interobserver variability. One of the observers repeated the investigation of the records after 2 weeks to evaluate intraobserver variability. The linear regression analysis was used to evaluate the reproducibility of the measurements. The variability of the measurements of the strain and strain rate between the observers was within acceptable limits (the measured SE was 6.0% for the strain rate and 4.4% for strain). To determine the myocardial performance index (MPI), the duration from the closing of the mitral valve until the opening was measured (a). This was determined by the beginning and the end of two consequent trans-mitral flow waves. Then, the left systolic duration was determined by measuring the ejection wave duration (b). MPI was calculated as (a−b)/(b).

2.3 | Statistical analysis

All statistical analyses were performed by using statistical software IBM-SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY). Categorical variables were compared using the chi-square test. Mean values of continuous variables were compared between groups using the Student's *t* test if normally distributed, or the Mann-Whitney *U*statistic test if not, as tested by the Kolmogorov-Smirnov test. Similarly, the paired Student's *t* test and Wilcoxon's paired test were used to compare values before and after the levosimendan therapy, respectively. Bonferroni correction was used for paired comparisons. A *P* value <.05 was considered to be statistically significant.

3 | RESULTS

The baseline characteristics of the patients are given in Table 1. There were 12 patients with a history of hypertension and 8 patients with a history of diabetes mellitus. All patients were under angiotensin converting enzyme inhibitor and diuretic treatment. Fifteen patients had been using spironolactone, 5 were under amiodarone treatment, and only 3 were on low dose beta-blocker medication. The echocardiographic parameters variables of the patients before and after the infusion at the 72nd hour and one month are shown in Table 2. The infusion rate of levosimendan was decreased by half in 3 patients because they developed frequent polymorphic ventricular tachycardia with accompanying hypotension. Other than this, no severe complication was observed during levosimendan infusion. During the one month follow-up, there was neither death nor rehospitalization resulting from decompensated HF. Before levosimendan infusion, the functional capacity was NYHA class IV in 13 patients and class III in the remaining 9 patients. Although there was no significant improvement in functional capacity at the 72nd hour after infusion, amelioration was prominent in 20 of the patients at one month. However, the EF increased from 23 ±4.24% to 30.84 ±5.25% at the 72nd hour whereas it was 26.77 ±4.48% at one month. Although a slight decrease in EF was observed at one month, its values both at the 72nd and one month were significantly greater than baseline values ($P < .05$). The strain and strain rate values of both ventricles were lowest at baseline and highest at the 72nd hour (Figure 1). The mitral inflow (E) speed was significantly decreased. The E/Ea ratio was also significantly reduced at the 72nd hour and one month. The decrease in MPI was prominent in both ventricles at the 72nd hour. At one month, although slightly increased in both ventricles, the MPI values were still lower than at baseline. Pulmonary artery pressure was indirectly estimated by tricuspid regurgitation flow. It was lowest at the 72nd hour (37.50 ±11.3 mm Hg) and slightly increased at one month. TAPSE was lowest at baseline and highest at the 72nd hour (Table 2).

TABLE 1 Baseline characteristics of patients before levosimendan infusion

	N = 22
Age (years)	53 ±12
NYHA functional class, (*n*)	
III	13
IV	9
Systolic blood pressure (mm Hg)	96 ±8
Diastolic blood pressure (mm Hg)	76 ±12
Heart rate (bpm)	88 ±12
Medication *n* (%)	
Diuretic	22 (100%)
ACE/ARB	22 (100%)
Beta-blocker	3 (13.6%)
Spironolactone	15 (68.8%)
Amiodarone	5 (22.5%)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; NYHA, New York Heart Association.

4 | DISCUSSION

To the best of our knowledge, this is the first report of serial measurements of STE-derived S/SR to evaluate the effects of levosimendan in patients with decompensated HF. STE-derived S/SR variables showed that levosimendan therapy improved LV systolic and diastolic function in patients with decompensated HF. This improvement was especially marked at the 72nd hour after infusion. Moreover, levosimendan has also favorable short-term effects on right ventricular function. We also observed some decline in the effect of levosimendan at one month.

The LV function can be evaluated using EF, which does not enable performing quantitative analysis of wall motion dynamics. However, the strain rate correlates more closely with invasively determined variables of global function.[20] Thus, this technique may be used instead of EF to quantify global LV function. It can demonstrate the myocardial tissue deterioration long before EF starts decreasing. In our study, various echocardiographic variables were evaluated in patients with decompensated HF who received levosimendan as an inotropic agent. Consistent with previous studies, significant improvement was observed in left ventricular end-systolic volume (LVESV), LVEF, and diastolic parameters such as E/Ea.[21] A few echocardiographic studies have analyzed the effect of levosimendan on LV function. Navarri et al. showed an increase in LVEF and LV torsional dynamics in patients with acute HF after levosimendan therapy.[22] Unlike ours, half of the patients in their study had nonischemic dilated cardiomyopathy. A significant reduction in brain natriuretic peptid and circulating proinflammatory cytokine levels were also noted after levosimendan therapy. This reduction was accompanied by a significant increase in LVEF and LV twisting. In another study, performing serial measurements of STE-derived S/SR in ST-elevation myocardial infarction patients developing acute HF, and treated with levosimendan,[18] Huseybe et al., found STE derived S/SR to be sensitive indicators of changes in LV function. We evaluated serial measurements of S/SR in nonischemic dilated cardiomyopathy patients with signs of decompensation and observed a significant improvement in the strain and strain rate of both left and right ventricles. The favorable effects of levosimendan on systolic and diastolic variables were at a maximum at the 72nd hour. The significant increase in EF was consistent with the significant increase in the strain and strain rate variables that indirectly reflect the LV contractility. Continuation of these positive effects with a slight decrease until the end of the first month was also noteworthy. Improving systolic function is a priority in the management of HF patients. Although diastolic dysfunction is generally overlooked, it is also of clinical significance in terms of both symptoms and prognosis. Diastolic dysfunction may cause HF symptoms even in patients with preserved LV function.[23] Furthermore, the prognostic value of diastolic dysfunction has already been demonstrated via previous randomized clinical trials.[24] Other myofilament calcium sensitizers are bound to the troponin C calcium complex during both systole and diastole with improvement of systolic function but possible impairment of diastolic function as a result of the facilitation of cross-bridging at diastolic calcium levels.[25] Binding of levosimendan to troponin C is dependent on the cytosolic calcium concentration and increases during systole but

TABLE 2 Echocardiographic parameters before and after levosimendan therapy

	Baseline	72nd hour	One month	*P* value
Heart rate (bpm)	88 ± 12	92 ±10	86 ±15	NS
SBP (mm Hg)[#]	96 ±8	102 ±6	105 ±6	<.05[a,c]
DBP (mm Hg)	76 ± 12	78 ± 21	75 ± 15	NS
NYHA (*n*)				<.05[b,c]
II			20	
III	13	15	2	
IV	9	7	0	
Weight (kg)[*]	78 ± 31	75 ± 28	71 ± 29	.03[a,b,c]
EDVI (mL)	110 ± 13.34	107 ± 12.45	105 ± 14.21	NS
ESVI (mL)[¶]	84.19 ± 10.78	74 ± 8.90	77 ± 12.54	<.05[a,b,c]
LVEF %[€]	23 ± 4.24	30 ± 5.25	26 ± 4.48	<.05[a,b,c]
LAD (cm)	5.3 ±0.87	5.2 ± 0.92	5.3 ± 0.77	NS
E wave speed[£] (cm/s)	1.1 ± 0.21	0.78 ± 0.19	0.86 ± 0.21	<.05[a,b,c]
DT (ms)[*]	209 ±88	230 ± 67	221 ± 75	<.05[a,b,c]
Ea[#]	5.96 ±2.4	6.70 ± 2.63	5.21 ±2.14	<.05[a,b,c]
E/Ea[&]	21.34 ±6.61	13.78 ±5.48	18 ±5.97	<.05[a,b,c]
LV MPI[θ]	0.99 ±0.54	0.68 ±0.34	0.90 ±0.41	<.05[a,b,c]
LV MPI Td[β]	1.12 ± 0.49	0.79 ± 0.41	0.84 ±0.53	<.05[a,b,c]
LV-S strain rate[γ]	6.54 ± 2.28	10.13 ± 2.91	8.12 ±2.64	<.05[a,b,c]
LV-S strain %[λ]	11 ±3.21	17 ±3.44	13.33 ±2.61	<.05[a,b,c]
RV MPI[ϭ]	0.89 ±0.39	0.63 ±0.33	0.79 ±0.36	<.05[a,b,c]
RV MPI Td[ϰ]	1.12 ± 0.44	0.84 ±0.35	0.95 ±0.42	<.05[a,b,c]
RV-S strain rate[ь]	2 ± 0.65	2.64 ±0.73	2.2 ±0.55	<.05[a,b,c]
RV-S strain %[ת]	20 ± 6.6	26 ±7.1	22 ±6.8	<.05[a,b,c]
RV TAPSE[ר]	16.24 ±3.71	21.34 ±4.45	18.15 ±3.56	<.05[a,b,c]
PAP (mm Hg)[ש]	50.16 ±15.2	37.50 ±11.3	42.59 ±13.4	<.05[a,b,c]

Abbreviations: DBP, diastolic blood pressure; DT, deceleration time; E, early filling velocity; EDVI, end diastolic volume index; EF, ejection fraction; Ea, tissue Doppler early myocardial velocity; ESVI, end systolic volume index; LAD, left atrial diameter; LV MPI, left ventricle myocardial performance index; LV MPI Td, left ventricle myocardial performance index calculated by tissue Doppler method; LV-S strain %, left ventricle systolic strain %; LV-S strain rate, left ventricle systolic strain rate; NYHA, New York Heart Association; PAP, pulmonary artery pressure; RV MPI, right ventricle myocardial performance index; RV MPI Td, right ventricle myocardial performance index by calculated tissue Doppler method; RV-S strain rate, right ventricle systolic strain rate; RV-S strain %, right ventricle systolic strain %; RV TAPSE, tricuspid annular plane systolic excursion; SBP, systolic blood pressure.

Post hoc analysis: [*]*P* = .012 for a, and *P* = .007 for c, [*]*P* = .007 for c, [¶]*P* = .013 for a and *P* = .015 for c, [€]*P* = .001 for a, and *P* = .015 for c, and *P* = .010 for b,[£]*P* = .004 for a and *P* = .011 for c, [*]*P* = .002 for a and *P* = .008 for c and *P* = .014 for b, [#]*P* = .015 for a,[&]*P* = .005 for a and *P* = .014 for c, *P* = .008 for b, [θ]*P* = .001 for a and *P* = .007 for b, and *P* = .014 for c, [β]*P* = .013 for a, [γ]*P* = .001 for a, and *P* = .010 for b, and *P* = .015 for c, [λ]*P* = .002 for a, and *P* = .012 for b, and *P* = .015 for c, [ϭ]*P* = .001 for a, and *P* = .008 for b, and *P* = .014 for c, [ϰ]*P* = .011 for a, [ь]*P* = .001 for a, and *P* = .014 for b, [ת]*P* = .002 for a, and *P* = .015 for b, [ר]*P* = .014 for a, [ר]*P* = .004 for a, [ש]*P* < .001 for a, and *P* = .013 for c.

[a] *P* < .05 for comparison between baseline and 72nd hour.

[b] *P* < .05 for comparison between 72nd hour and one month.

[c] *P* < .05 for comparison between baseline and one month.

is relatively unchanged during diastole.[26] This mechanism may be the reason for the parallel enhancement of myocardial contractility and improvement of LV diastolic function without promoting arrhythmogenesis or alteration of myocardial oxygen demand in experimental studies.[27] Recent clinical studies also revealed that levosimendan does not cause any deterioration in diastolic function.[28] Moreover, Parissis et al. demonstrated that an improvement in the parameters of LV diastolic function such as mitral E/A and E/E' ratio after levosimendan therapy.[29] Hasenfuss et al. reported an increase in LV deceleration time and isovolumic relaxation time (IVRT) after levosimendan therapy.[12] We also observed a decrease in E and E/Ea ratio and a prolongation in deceleration time (DT) and IVRT, consistent with results of previous studies. The usefulness of MPI in the evaluation of systolic and diastolic function is well-known.[30] MPI decreases with increasing myocardial performance. A significant MPI decrease in both ventricles, with prolongation of the diastolic filling phase and of the ejection time, were the other prominent findings. All of these changes will essentially improve low cardiac output and provide better coronary perfusion.

However, favorable effects of levosimendan were also prominent on the right ventricle. It was shown that systolic velocity and strain best correlates with invasively determined right ventricular stroke volume and dynamically tracked changes in right ventricular function.[31] Strain rate and strain enabled quantitative analysis of regional right ventricular systolic function in a healthy population as well as in various pathologies.[32,33] In our study, a slight increase in LV function most likely resulted in a decrease in pulmonary capillary wedge pressure, leading to a decrease in the RV afterload. This can be the reason for

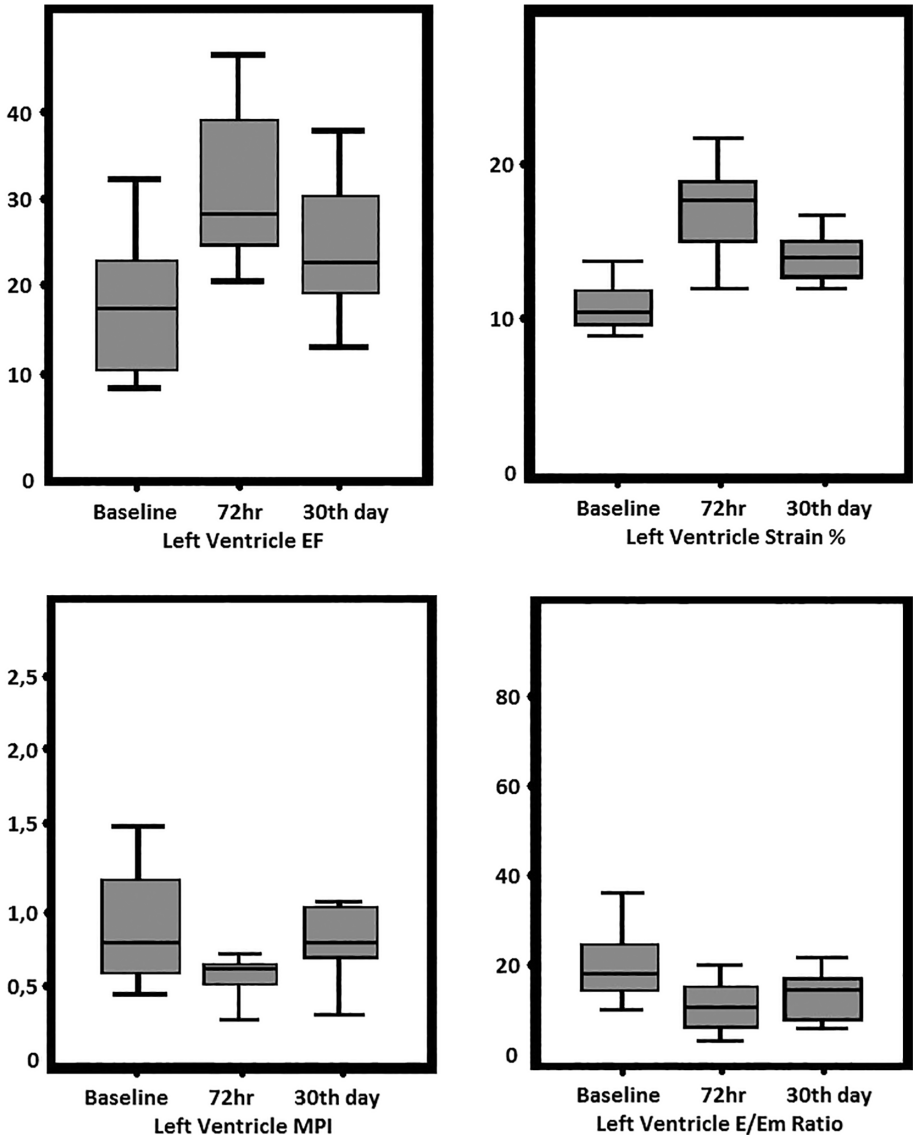

FIGURE 1 Demonstration boxes-and-whiskers plots showing the positive effects of levosimendan on left ventricular echocardiographic ejection fraction (EF), strain, myocardial performance index (MPI), and E/Em ratio (the box includes the second and third quartiles, and the whiskers extend to the range. The horizontal line dividing the box shows the median)

the increase in the output and decrease in the RV MPI. Consequently, our study clearly indicates that levosimendan had favorable effects on systolic and diastolic functions of both ventricles. Improvement in the echocardiographic variables was more prominent at the 72nd hour but, despite a slight decrease, the favorable effects of levosimendan were still obvious at one month.

5 | STUDY LIMITATIONS

The number of patients included in our study was small because our study population was limited to patients with nonischemic dilated cardiomyopathy. Therefore, as the small sample size in this study precludes any valid subgroup analysis, we did not identify any confounders that may have interacted with outcome. In addition, S and strain rate variables can be affected by environmental artifacts. We tried to overcome this limitation by narrowing the image window and increasing the frame rate. Another limitation was low EF that results in the suboptimal evaluation of apical segments. Therefore, we evaluated basal and mid segments in apical four and two chamber views.

6 | CONCLUSION

STE can successfully complete conventional echocardiography to evaluate patients with dilated cardiomyopathy who are treated with levosimendan.

CONFLICT OF INTEREST

All authors declare that no potential, perceived, or real conflict of interest exists in connection with this manuscript.

ORCID

Tuncay Kırış http://orcid.org/0000-0001-9793-718X

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How to cite this article: Kırış T, Avcı E. Short-term effects of levosimendan on strain/strain rate markers in patients with nonischemic dilated cardiomyopathy. *J Clin Ultrasound*. 2018;46:527–532. https://doi.org/10.1002/jcu.22627