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Comparative assessment of the effects of dobutamine and levosimendan on right ventricular ejection fraction in patients with biventricular heart failure

Aim	The primary objective of this study was to comparatively assess the effects of levosimendan and dobutamine on RVEF, right ventricular diastolic function, and hormonal balance in patients with biventricular heart failure. The secondary objective was to investigate the relationship between the RVEF and the peak systolic velocity (Sa), an indicator of right ventricular systolic function, as measured by tissue Doppler echocardiography from the tricuspid annulus, and by the tricuspid annular plane systolic excursion (TAPSE).
Material and Methods	The population of this cross-sectional, single-center, prospective study was comprised of 81 patients, who between December 2019 and January 2022, applied to the study health institution with diagnosis of ADHF. The study sample included 67 biventricular heart failure patients with left ventricular ejection fraction (LVEF) <35% and RVEF <50%, as measured by the ellipsoidal shell model, and who met the other study inclusion criteria. Of these 67 patients, 34 were treated with levosimendan, and 33 were treated with dobutamine. RVEF, LVEF, Sa, peak early (Ea) and peak late (Aa) annular velocities, Ea/Aa ratio, TAPSE, systolic pulmonary artery pressure (SPAP), n-terminal pro-brain natriuretic peptide (NT-pro BNP), and functional capacity (FC) were measured before treatment and at 48 hrs of treatment. The within group pre- and post-treatment differences (Δs) of these variables were compared.
Results	RVEF, SPAP, and BNP, and FC significantly improved in both treatment groups ($p<0.05$ for all). Sa ($p<0.01$), TAPSE ($p<0.01$), LVEF ($p<0.01$), and Ea/Aa ($p<0.05$) improved only in the levosimendan group. The pre- and post-treatment Δs for RVEF, LVEF, SPAP, Sa, TAPSE, FC, and Ea/Aa were higher in the levosimendan group than in the dobutamine group ($p<0.05$ for all).
Conclusion	Compared to dobutamine, levosimendan produced greater improvement in right ventricular systolic and diastolic function in patients with biventricular heart failure and in need of inotropic therapy support.

Keywords	Levosimendan; dobutamine; heart failure; right ventricular systolic dysfunction
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Introduction

Heart failure (HF) is currently one of the most significant causes of mortality and morbidity [1, 2]. Although advances have been made in the treatment of HF, the morbidity and mortality rates associated with acute decompensated HF (ADHF) remain high [3]. Right heart failure (RHF) is more lethal than left heart failure (LHF). Therefore, right ventricular (RV) support is important in HF, and improvement in its functions is a desired outcome [4, 5]. Unlike other inotropic agents, levosimendan has been shown in many studies to improve cardiac function in this patient group by increasing myocardial contractility without increasing intracellular calcium [6].

The number of studies on the effects of levosimendan treatment on RV function is limited [7, 8]. Echocardiographic evaluation of RV function, including RV ejection fraction (RVEF), is difficult due to the complex geometric shape of the RV. Semi-quantitative assessment of RV function without volume determination is one of the most common methods used to circumvent this problem. The ellipsoidal shell model is considered the best method for determining the volume of the RV with two-dimensional echocardiography [9]. With this in mind, the objective of this study was to compare the effects of levosimendan and dobutamine treatment on RV function, including RVEF, in patients with ADHF.

Material and Methods

The population of this cross-sectional, single-center, prospective study was comprised of 81 patients, who applied to this medical institution between December 2019 and January 2022 with a diagnosis of ADHF. The study sample was comprised of 67 biventricular HF patients,

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who had New York Heart Association (NYHA) functional class III or class IV symptoms, and with LVEF <35%, and RVEF <50%, as calculated using the ellipsoidal shell model detailed below. The indication for positive inotropic therapy was determined by the primary physician consistent with the recommendations of the European Society of Cardiology. The first screening of the patients to determine whether the inclusion criteria were met was performed within 2 hours of making the decision for inotropic therapy. The initial echocardiographic examination was performed by an independent, experienced cardiologist who was blinded to the study protocol and to the randomization prior to initiation of the treatment. Patients who were pregnant, with atrial fibrillation, a history of hypersensitivity to levosimendan or dobutamine and their metabolites, 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 block, restrictive or hypertrophic cardiomyopathy, structural heart valve disease, or acute coronary syndrome were excluded from the study. Information about n-terminal pro-brain natriuretic peptide (NT-pro BNP) and weight, along with demographic and clinical characteristics, such as age, gender, previously used medications, and blood pressure were obtained before treatment and at 48 hours of the treatment.

Tissue Doppler echocardiography of the tricuspid annular movement, tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary artery pressure (SPAP), and RVEF (GE-Vivid 4 with a 3.5 MHz transducer; GE, Milwaukee, WI, USA) and standard echocardiographic examination were performed in all patients before the treatment and at 48 hours of treatment. In the apical 4-champer view, a 5 mm sample volume of pulsed wave Doppler was placed at the point where the tricuspid annulus intersects the anterior tricuspid leaflet. Peak systolic (Sa), peak early (Ea) and late (Aa) diastolic annular velocities (cm/sec) were calculated for the RV tissue Doppler imaging (TDI). In the apical four-chamber view, the TAPSE value (mm) was obtained by using the M-mode tracing from the point where the tricuspid annulus meets the lateral free wall. Conventional echocardiographic examination, including M-mode and two-dimensional echocardiography were performed in all patients. After localizing the tricuspid regurgitation with Doppler color flow imaging, the peak tricuspid jet flow velocity was calculated using continuous-wave Doppler ultrasound. Afterwards, the pressure gradient between the right atrium and the RV was calculated using the Bernoulli equation [10], and the SPAP was obtained by adding the mean right atrial pressure. The mean right atrial pressure was estimated according to the diameter of the inferior vena cava and respiratory variation, and the pressure change between the RV and right atrium. 33 patients were given dobutamine and the remaining 34 were given levosimendan. Dobutamine infusion was administered at a dose range of 5–15 μg/kg/min. The dose was adjusted according to the patient's heart rate, hemodynamic response, and systolic blood pressure. Levosimendan was administered first as a loading dose of 12–24 μg/kg for 10 min and then as infusion therapy at a dose range of 0.05–0.2 μg/kg/min. Dose titration was performed in patients who tolerated the treatment.

The local ethics committee approved the study protocol. Informed consent was obtained from all patients included in the study.

Calculation of the RV Ejection Fraction

RV volumes were calculated using a formula based on the ellipsoidal shell model, V=2/3Pd. P, defined as the area, was measured manually through the border scanning method by modifying the apical four-chamber projection and separately for systole and diastole. Septomarginal trabeculae were included in the scanned area. The best RV cavity area was obtained by rotating the transducer in the apical four-chamber projection clockwise 15–20°. D, the diameter in the volume equation, was measured from the parasternal short axis view. After imaging the mitral valve orifice, the transducer was tilted in the upward direction to ensure visualization of the aortic valve cusps. Thus, the RV outflow tract was visualized from this angle as curved around the aorta, and the tricuspid valve was on one side of the aorta and the pulmonic valve on the opposite side. The longest distance between the point where the tricuspid ring intersected the RV lateral wall and the RV outflow tract under the pulmonic valve was taken as the d value of the equation. P, i.e., the RV area, and d, i.e., the longest diameter of the RV, were measured separately for systole and diastole, and the RV ejection fraction was calculated from the difference in diastolic and systolic volumes [9].

Statistical Analysis

Statistical analyses of the collected research data were performed with the SPSS 24 software package (Statistical Package for Social Sciences for Windows, Version 24.0, IBM Corp., Armonk, NY, U. S. A., 2016). The distribution of patients' gender and medications were expressed as frequencies, whereas the patients' age, weight, body mass index (BMI), echocardiographic measurements, and laboratory test results were expressed as mean±standard deviation (SD).

Paired t-tests and Pearson's chi-squared tests were used to compare the levosimendan and dobutamine groups in terms of demographic characteristics, echocardiographic measurements, laboratory test results, and medication histories. Paired t-tests were used to evaluate pre-treatment and post-

Table 1. Demographic characteristics of the patients and pre-treatment medications, laboratory values, and echocardiographic measurements

Demographic and clinical characteristics	Levo-simendan Group (n=34)	Dobu-tamine Group (n=33)	p value
Gender (M/F)	18/16	20/13	0.527
Age (yrs)	66.9±6.3	67.1±11.7	0.917
Weight (kg)	67.5±11.5	66.5±12.1	0.490
BMI (kg/m²)	24.9±4.7	24.5±4.2	0.750
FC	3.8±0.3	3.7±0.5	0.352
Echocardiographic measurements			
LVEF (%)	24.3±5.5	23.9±5.1	0.751
RVEF (%)	30.6±4.4	30.7±5.4	0.890
TAPSE (mm)	10.30±1.54	10.49±2.01	0.665
SPAP (mmHg)	52.59±8.12	52.73±9.11	0.948
RV TDI			
Sa (cm/s)	8.5±1.9	9.2±2.7	0.191
Ea (cm/s)	8.1±1.1	8.2±1.7	0.884
Aa (cm/s)	11.7±2.0	11.3±2.3	0.458
Ea/Aa	0.70±0.1	0.75±0.23	0.347
Laboratory data			
Urea (mg/dl)	54.5±18	53.6±18	0.839
Creatinin (mg/dl)	1.07±0.3	1.07±0.2	0.894
Sodium (mmol/L)	135.4±4.8	134.4±4.3	0.378
Potassium (mmol/L)	4.5±0.6	4.3±0.8	0.344
Calcium (mmol/L)	8.5±0.7	8.6±0.4	0.615
Hematocrit (%)	37.9±4.9	37.1±4.3	0.473
Hemoglobin	12.8±1.5	12.7±1.3	0.749
White blood cell count	7.3±2.0	8.3±2.7	0.087
Platelet count	257.6±86.5	263.5±123	0.820
NT-pro BNP (ng/ml)	16.3±10.1	16.7±10.1	0.938
High-density lipoprotein (mg/dl)	31.1±13	31.5±9.9	0.897
Low density lipoprotein (mg/dl)	98.6±43.7	95.0±32.6	0.703
Total cholesterol (mg/dl)	156.3±48.2	151.9±48.4	0.768
Triglycerides (mg/dl)	121.6±41.6	107.7±36.2	0.258
Medications			
Asa	31	29	0.659
Ace	31	29	0.659
Beta	19	25	0.087
Statin	14	18	0.273
Aldactone	16	14	0.703
Digoxin	30	21	0.068
Furosemide	12	7	0.201
Thiazide	24	26	0.441

Data are numbers or mean±SD. BMI, body mass index; RVEF, right ventricular ejection fraction; LVEF, left ventricular ejection fraction; SPAP, pulmonary artery systolic pressure; FC, functional capacity;TAPSE, tricuspid annular plane systolic excursion; RV TDI, right ventricular tissue Doppler imaging; Sa, tricuspid annular peak systolic; Ea, tricuspid annular early diastolic velocity; Aa, tricuspid annular late diastolic velocity.

treatment differences (Δs) between the levosimendan and dobutamine groups for RVEF, LVEF, SPAP, Sa, Aa, Ee, NT-pro BNP, TAPSE, Ee/Aa ratio, and FC parameters. In addition, correlation analysis was performed to investigate the relationship between the changes in ΔRVEF and other variables. Probability (p) values of <0.05 were deemed to indicate statistically significance.

Results

Of the initial 81 patients, five had renal dysfunction, and three had atrial fibrillation. These patients were excluded from the study. Additionally, three patients were excluded because their echocardiographic imaging results were inconclusive, and another three patients were excluded because they developed hypotension during treatment. The remaining 67 patients were randomized into two groups of 34 patients (levosimendan group) and 33 patients (dobutamine group).

Baseline characteristics between the two groups

As can be seen in Table 1, there was no significant differences between the levosimendan and dobutamine groups in terms of pre-treatment epidemiological data, laboratory results, and echocardiographic measurements (p>0.05 for all variables).

The changes in the RV function detected by echocardiography

The comparison of pre- and post-treatment RVEF values of the levosimendan (30.6±4.4 vs. 37.0±5.2, p<0.001) and dobutamine (30.7±5.4 vs. 33.2±6.2, p=0.004) groups revealed significant increases in the RVEF values of both groups (Table 2). The LVEF values significantly improved in the levosimendan group (24.3±5.5 vs. 29.9±8.8, p<0.001) after the treatment, but not in the dobutamine group (23.9±5.1 vs. 25.6±5.5, p=0.058). The Sa wave, one of the RV TDI variables, increased in the levosimendan group (8.5±1.9 vs. 10.4±2.3, p<0.0001), but not in the dobutamine group (9.2±2.7 vs. 9.8±2.6, p=0.096). On the other hand, the Ea wave significantly increased in both groups, whereas the Aa wave did not. In addition, the Ea/Aa ratio significantly increased only in the levosimendan group (0.70±0.1 vs. 0.78±0.1, p:0.004), but not in the dobutamine group (0.75±0.2 vs. 0.74±0.2, p:0.782). Post-treatment, in both the levosimendan and dobutamine groups, there was a significant decrease in NT-pro BNP [(16.3± 10.1 vs. 6.6±7.5, respectively, p=0.011) and (16.7±10.1 vs. 8.3±6.9, respectively, p<0.0001)] along with a significant improvement in the FC values [(3.7±0.4 vs. 3.2±0.4, respectively, p<0.001) and (3.8±0.4 vs. 2.7±0.6, respectively p<0.001)] (Table 2) The comparative analysis of the levosimendan and dobutamine groups in terms of Δs

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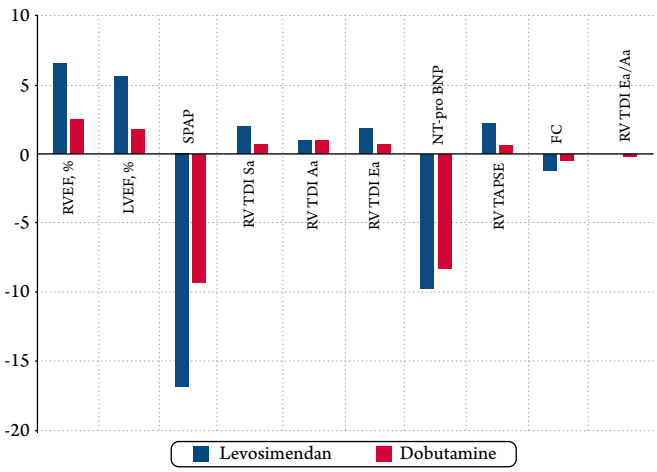
Table 2. Changes in the echocardiographic measurements, NT-pro BNP, and FC for the levosimendan and dobutamine groups

Variable	Levosimendan Group			Dobutamine Group		
	Pre-treatment	Post-treatment	p value	Pre-treatment	Post-treatment	p value
RVEF (%)	30.6±4.4	37.0±5.2	<0.001	30.7±5.4	33.2±6.2	0.004
LV EF (%)	24.3±5.5	29.9±8.8	<0.001	23.9±5.1	25.6±5.5	0.058
SPAP (mmHg)	52.59±8.12	35.82±7.30	<0.001	52.73±9.11	43.58±9.16	<0.001
Sa (cm/s)	8.5±1.9	10.4±2.3	<0.001	9.2±2.7	9.8±2.6	0.096
Aa (cm/s)	11.7±2.0	12.7±2.2	0.007	11.3±2.3	12.2±2.5	0.008
Ea (cm/s)	8.1±1.1	9.9±2.1	<0.001	8.2±1.69	8.8±2.5	0.045
Ea/Aa	0.70±0.1	0.78±0.1	0.004	0.75±0.2	0.74±0.2	0.782
NT-pro BNP (ng/ml)	16.3±10.1	6.6±7.5	<0.001	16.7±10.1	8.3±6.9	0.011
TAPSE (mm)	10.3±1.5	12.5±2.3	<0.001	10.5±2.0	10.9±2.3	0.077
FC (NYHA)	3.8±0.4	2.7±0.6	<0.001	3.8±0.4	3.2±0.4	<0.001

Data are mean±SD. See Table 1 footnote for abbreviations.

Figure 1. Comparison of the effects of levosimendan and dobutamine on echocardiographic parameters, hormonal level and functional capacity



between the pre-treatment and post-treatment RVEF, LVEF, SPAP, Sa, Aa, Ea, Ea/Aa, NT-pro BNP, TAPSE, and FC values revealed that the recovery in the levosimendan group was more prominent in all categories except for NT-pro BNP and the RV Aa wave (Table 3). The effect of the treatment on echocardiographic variables, NT-pro BNP concentrations, and the percent change in FC values was more prominent in the levosimendan group (Figure 1).

Correlation analysis was employed to investigate the relationships between ΔRVEF and ΔLVEF, ΔSa, ΔTAPSE, ΔSPAP, Δ NYHA functional classification, and RV ΔEa/Aa in the levosimendan group. Consequentially, a weak positive correlation was found between the ΔRVEF and ΔLVEF (r=0.314, p=0.01), and a moderate positive correlation was found with ΔTAPSE (r=0.455, p<0.001) and with ΔSa (r=0.565, p<0.001). The correlation between ΔRVEF and ΔSPAP was weak and negative, albeit not statistically significant (r=–0.151, p=0.224). In addition, there was a moderate positive correlation (r=0.439, p<0.001) between ΔRVEF and the degree of heart failure determined

Table 3. Comparison of post-treatment – pre-treatment values of echocardiographic measurements, hormone concentrations, and FC values for the levosimendan and dobutamine groups

Variable	Levosimendan Group	Dobutamine Group	p value
RV ΔEF (%)	6.5±3.7	2.5±1.6	<0.001
LV ΔEF (%)	5.6±2.7	1.8±0.1	0.006
ΔSPAP	-16.8±7.0	-9.2±8.7	<0.001
RV ΔSa	1.9±1.4	0.6±0.2	0.002
RV ΔAa	0.9±1.9	0.9±1.8	0.870
RV ΔEa	1.8±1.7	0.6±0.7	0.009
ΔNT-pro BNP	-9.7±9.6	-8.3±17	0.700
ΔTAPSE	2.2±1.9	0.5±0.5	<0.001
ΔFK	-1.2±0.6	-0.5±0.50	<0.001
RV ΔEa/Aa	0.08±0.1	-0.01±0.1	0.030

Data are mean±SD. Δ = post-treatment – pre-treatment value. See Table 1 footnote for abbreviations.

Table 4. Correlation analysis of the Δ values of RVEF with LVEF, TAPSE. Sa, E/A. SPAP, FC and various other variables

Variables	Correlation with Δ RVEF	
	r value	p value
ΔLVEF	0.314	0.01
ΔTAPSE	0.455	<0.001
ΔSa	0.56	<0.001
ΔSPAP	–0.151	0.224
ΔRV Ea/Aa	0.718	<0.001
NYHA functional classification	0.439	<0.001

See Table 1 footnote for abbreviations.

in accordance with the NYHA functional classification, and there was a highly significant, positive correlation between the ΔRVEF and RV Δ Ea/Aa (r=0.718, p<0.001).

Discussion

RV systolic and diastolic function are important indicators for mortality and for nonfatal cardiac events in

patients with advanced heart failure [7, 8]. Many studies have shown good correlations between RVEF values, determined using the "ellipsoidal shell model", which is an easily applicable method that involves simple mathematical operations, and RVEF values determined using magnetic resonance imaging (MRI) [10]. In addition, the ellipsoidal shell model is easy to use for calculating RVEF when used by echocardiographers that are experienced in two-dimensional echocardiography. Moreover, in terms of accuracy, the ellipsoidal shell model provides results that are comparable to the values measured by three-dimensional echocardiography [11, 12].

The findings of this study suggest that the ellipsoidal shell model can be used to measure RVEF in hospitals where the use of cardiac MRI is not common, such as the institution where this study was conducted. In this study, the effects of levosimendan and dobutamine treatments on the RVEF and the LVEF, RV tissue Doppler variables, NT-pro BNP concentrations, SPAP values, and FC values were compared. Significant improvements were observed in the LVEF, Sa wave, Ea wave, TAPSE values, and Ea/Aa ratios in the levosimendan group. In addition, statistically significant improvements were observed in the NT-pro BNP, SPAP and FC values in both groups. These findings are consistent with the findings reported by Duygu et al. [13]. In the current study, the increase in RVEF was greater in the levosimendan group. This finding can be partially explained by the positive effect of levosimendan on the LVEF [14, 15]. The mechanical effect of levosimendan on the RV and on pulmonary vascular resistance, which is decreased due to the vasodilator effect of levosimendan on the pulmonary bed, might have contributed to the greater improvement in RVEF in the levosimendan group compared to the dobutamine group [16]. It has also been demonstrated in animal studies that levosimendan directly increases RV contractility [17]. In their controlled studies that included levosimendan and placebo groups, Kaşıkçıoğlu et al. [7] and Parissis et al. [8] demonstrated positive effects of levosimendan on RV systolic and diastolic function. In the current study, dobutamine was used instead of a placebo. Consistent with the results of the above mentioned studies, positive effects of levosimendan on RV systolic function were demonstrated. In addition, RVEF, obtained using the ellipsoidal shell model, was moderately correlated with the Sa wave and TAPSE values, which are indicators of RV systolic function. This finding may further support the use of the ellipsoidal shell model for measuring RVEF. The decrease recorded in SPAP is noteworthy, since it favors the use of levosimendan. It is known that dobutamine treatment improves RV-pulmonary artery coupling by decreasing pulmonary vascular resistance and by increasing RV contractility [18]. On the other hand, the fact that levosimendan improves SPAP more than dobutamine may be attributed to the vasodilation effect that levosimendan exerts on the pulmonary vascular bed and the improvement it provides in LV systolic function [19]. The positive effect of levosimendan on RV systolic function detected in this study was observed also on RV diastolic function. The increase in the Ee/Aa ratio, which was measured from the tricuspid annulus and is thought to be independent of preload, was also found to be more significant in patients receiving levosimendan compared to that in patients receiving dobutamine. Although many studies have examined the effects of levosimendan and dobutamine on LV diastolic function, studies on their effects on RV diastolic function are sparse [20]. The findings of this study indicated that levosimendan provided greater improvement in RV diastolic function than did dobutamine. This finding may be attributed to the improvement levosimendan provides in RV systolic function and LV filling pressures as well as to the effective utilization of intracellular calcium during diastole.

Limitations of the Study

The study's single-center design is one of its major limitations. Secondly, the sample size was small. Thirdly, the quality of the echocardiography images of some patients included in the study was substandard. Lastly, Swan-Ganz catheterization could have been performed to have better understood the hemodynamic effects of both levosimendan and dobutamine. In that way, directly measured hemodynamic data such as pulmonary vascular resistance index, pulmonary capillary wedge pressure, and cardiac index could have been compared with data obtained by echocardiography.

Conclusion

The findings of this study indicated that levosimendan provided more improvement of RV systolic and diastolic function in ADHF patients with biventricular heart failure and in need of inotropic therapy support than did dobutamine. In addition, a significant relationship was found between RVEF, which was measured using the ellipsoidal shell model, and the Sa and TAPSE values. Thus, RVEF measurements based on the ellipsoidal shell model can be considered feasible and reliable for use in health institutions where cardiac MRI is not widely available, provided that the analysis is performed by experienced echocardiographers.

No conflict of interest is reported.

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