Impact of levosimendan on right ventricular functions by using novel tissue Doppler derived indices in patients with ischaemic left ventricular failure

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Abstract

Background: Right ventricular (RV) dysfunction complicates advanced left ventricular (LV) heart failure (HF) and contributes to a poor prognosis. Levosimendan is a positive inotropic agent improving cardiac contractility without increasing myocardial oxygen consumption in HF.

Aim: To evaluate the effect of levosimendan therapy on RV systolic function, by using derived tissue Doppler imaging (TDI) in patients with ischaemic HF.

Methods: The study consisted of 30 patients with HF who were admitted to our hospital due to new onset of decompensated HF, having LV ejection fraction < 40%, with functional status class III–IV, according to the New York Heart Association (NYHA). TDI-derived systolic velocities of tricuspid annulus (isovolumic myocardial acceleration [IVA], peak myocardial velocity during isovolumic contraction [IVV], peak systolic velocity during ejection period [Sa]) and diastolic indices (early [Ea] and late diastolic [Aa] velocities, Ea/Aa, E/Ea ratios and myocardial performance index [Tei index]) were measured. 72 hours after treatment, all measurements were re-evaluated.

Results: Considering TDI-derived systolic indices of the RV, IVA and IVV increased significantly, whereas Tei index decreased, after the therapy. Also, there was a significant decrease in serum levels of B-type natriuretic peptide. No significant change was observed in TDI derived diastolic indices of the RV.

Conclusions: Levosimendan improves RV systolic function as expressed by TDI-derived parameters in patients with acute decompensated HF.

Key words: levosimendan, ischaemic heart failure, right ventricle, tissue Doppler imaging

INTRODUCTION

Levosimendan is a positive inotropic agent used for increasing myocardial contractility in acute left ventricular (LV) heart failure (HF). Levosimendan performs a positive inotropic effect by binding to cardiac troponin C and sensitising cardiac myofilaments to calcium [1]. It also exerts a vasodilatory effect in vascular smooth muscle cells, by inducing adenosine triphosphate-dependent potassium channel opening, primarily in the pulmonary arterial vasculature [2]. There are several inotropic agents which are currently available and widely used. However, their limitation is the tendency to increase mortality and risk of arrhythmias [3]. The therapeutic utility of levosimendan has been documented in several studies and its positive effect on systolic left HF is well-known. In a recent
The effect of levosimendan on right ventricular functions

In the present study, we aimed to assess the effect of levosimendan therapy on RV functions by using conventional and tissue Doppler imaging (TDI) derived echocardiographic parameters in patients with ischaemic HF.

**METHODS**

**Study design and patient population**

The study population consisted of 30 consecutive patients with ischaemic HF who were hospitalised due to New York Heart Association (NYHA) class III or IV symptoms and had documented LV ejection fraction (LVEF) < 40%, despite optimal medical therapy including diuretics, vasodilator agents and angiotensin converting enzyme inhibitors. Exclusion criteria were: significant valve stenosis and/or regurgitation more than mild degree, acute or chronic infectious or inflammatory diseases, recent myocardial infarction (≤ 8 weeks), active ischaemia, hepatic or renal insufficiency (serum creatinine > 2 mg/dL), use of anti-inflammatory agents, atrial fibrillation and other arrhythmias, systolic blood pressure < 90 mm Hg and having < 600 cc urine volume daily. The study protocol was approved by the local Ethics Committee of our institute and detailed written informed consent was obtained from each patient. The study was carried out according to the Declaration of Helsinki.

The patients were randomised to 48 h intravenous (i.v.) levosimendan therapy with a dose of 0.05 µg/kg/min, without a loading dose. Patients were under optimal medical therapy and none of them received parenteral positive inotropic medications except levosimendan. They were questioned about their cardiac symptoms and underwent a complete physical examination at baseline, 24 h after the initiation of the treatment, and at the end of the therapy. All patients underwent echocardiographic examination before levosimendan therapy and 24 h after the completion of the treatment.

**Echocardiographic measurements**

All patients were examined in the left lateral decubitus position by two-dimensional echocardiography (GE Vingmed, Vivid 7, Horten, Norway) using a 2.5 MHz transducer having TDI technology. Echocardiographic evaluation was performed by a cardiologist experienced in echocardiography. LV diameter and wall thickness were measured by M-mode echocardiography according to the recommendations of the American Society of Echocardiography [6]. From an apical four-chamber view, LVEF was calculated using modified Simpson’s method [6]. RV systolic diameter was measured from a parasternal long axis view by using M-mode [7]. The systolic pulmonary artery pressure (SPAP) was calculated by continuous-wave Doppler imaging from the peak velocity of the tricuspid regurgitation jet. The pressure gradient between the RV and the right atrium (RA) was calculated by using the Bernoulli equation ($ΔP = 4v^2$) [8]. SPAP was estimated by adding mean RA pressure, as estimated by the diameter of the inferior vena cava and its respiratory variation to the pressure gradient between the RV and the RA [9]. Tricuspid annular motion was recorded at the RV free wall from the apical four-chamber view. Tricuspid annular plane systolic excursion was measured by M-mode quantification at the junction of tricuspid valve with the RV free wall from the apical four-chamber view and maximum displacement during systole was evaluated [10]. RV outflow tract shortening fraction (RV OTSF) was obtained from the parasternal short axis view at the basal portion and was calculated by using RV end-diastolic outflow tract diameter (EDRVOTD) and RV end-systolic outflow tract diameter (ESRVOTD) (RV OTSF % = (EDRVOTD – ESRVOTD)/EDRVOTD [11]. Pulmonary flow acceleration time was measured as the time interval between the onset of the pulmonary flow and point of peak velocity, by using pulsed wave Doppler imaging from the parasternal short axis view [12]. Peak early (E) [m/s] and late diastolic (A) [m/s] tricuspid annular velocities were also analysed.

**Tissue Doppler echocardiography**

TDI was performed in the apical four-chamber view using a 5- to 10-mm sample volume placed on the tricuspid annulus lateral wall. Settings were adjusted for a frame rate between 120 and 180 Hz and a cineloop of 3–5 consecutive heart beats was recorded. TDI-derived systolic indices; peak myocardial velocity during isovolumic contraction (IVV) [m/s]; myocardial acceleration during isovolumic contraction (IVA) [m/s²], defined as the ratio of IVV divided by the acceleration time, and peak velocity during systolic ejection (Sa) [m/s] were measured, using pulsed wave TDI (Fig. 1). Peak early (Ea) [m/s] and late diastolic (Aa) [m/s] tricuspid annular velocities were also analysed. Myocardial perforation index was calculated as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time. All the measurements were calculated from three consecutive cycles and the average of three measurements was recorded.

**Biochemical analysis**

B-type natriuretic peptide (BNP) was measured by sandwich immunofluorescent assay technology with a fully automatic Advia Centavur-Cp machine.

**Statistical analysis**

The data was evaluated using descriptive statistics (mean, standard deviation). Qualitative data was compared using
Pre-treatment and post-treatment parameters were compared using Wilcoxon ranking test because of the failure of the establishment of parametric test conditions. For the evaluation of the correlation, Spearman correlation test was used because of the failure of the establishment of parametric test conditions. The results were considered significant when the p value was less than 0.05. Statistical analyses were done using Epi Info Version 3.5.1.

RESULTS
Baseline clinical and demographic characteristics of the patients before levosimendan therapy is presented in Table 1. All patients completed 48 h infusion therapy without dose-limiting effects. After the treatment, patients had significant clinical improvement, based on NYHA classification (Table 2). Moreover, a marked increase in LVEF of the patient group was observed at the end of the therapy (Table 2). There was a significant decrease in SPAP after the treatment.

Right ventricular TDI-derived systolic indices, IVV and IVA increased significantly after levosimendan therapy, demonstrating improvement in RV systolic function. Myocardial performance index, which is an indicator of systolic and diastolic function, was markedly decreased after the therapy.

Serum BNP level was reduced after the treatment, correlating with improvement in haemodynamic status. We obtained a significant negative correlation between LVEF and serum BNP level (r = –0.36, p = 0.045). Regarding RV diastolic indices, no significant change was observed after levosimendan therapy in the patient group (Table 2).

DISCUSSION
In the present study, we demonstrated a significant improvement in RV systolic function, based on TDI-derived parameters, in patients with acute ischaemic left HF. Levosimendan is a new option which improves myocardial contractility and induces coronary and peripheral vasodilation. Its therapeutic utility and positive effect on LV functions have been documented in previously published studies [13]. However, few studies have assessed its effect on RV functions [14].

Levosimendan induces improvement in LVEF and filling pressure, resulting in a reduction of pulmonary artery pressure. The positive effect of levosimendan on RV systolic function might have resulted partially from the improvement of LV systolic function [15]. Additionally, enhanced contractility of the RV can be attributed to vasodilating effects of levosimendan on the pulmonary arterial system, thus reducing pulmonary vascular resistance [16]. Levosimendan also induces coronary vasodilation, resulting in myocardial contractility [2].

In patients with HF, the systolic and diastolic functions of the RV are independent prognostic indicators [17, 18]. However, appropriate assessment of RV functions is problematic, due to its complex shape [19]. For this reason, it is quite difficult to achieve a proper evaluation of RV functions solely by using conventional echocardiographic parameters. Recently, the development in TDI techniques has enabled early detection of subendocardial dysfunction by evaluating myocardial velocities. This method has been presented as an additional, detailed modality alternative to conventional echocardiography [18–20].

Recently, a novel parameter, IVA, has been validated to be an alternative method and a relatively load-independent measure of RV systolic functions. IVA reflects the acceleration
Duygu et al. [22] and Kasıkcıoğlu et al. [23] demonstrated that levosimendan therapy significantly improves RV systolic function, based on TDI-derived systolic indices.

In the study performed by Parissis et al. [15], the impact of levosimendan on RV systolic and diastolic parameters was evaluated in 54 patients with advanced HF. They observed marked improvements in both systolic and diastolic functions of the RV due to levosimendan therapy. They also confirmed neurohormonal recovery as well as haemodynamic alteration, presented as a significant reduction of serum BNP level. Supporting these results, we suggested in our study that a decrease in serum BNP is an important benefit of levosimendan therapy, representing an anti-inflammatory modulation. It has been documented that levosimendan infusion has anti-inflammatory properties in decompensated HF, reducing circulating pro-inflammatory cytokines and soluble apoptosis mediators [24]. Additionally, the reduction of serum BNP level might be due to decreases in myocardial wall stress and LV filling pressure. Our data demonstrated a significant decrease of BNP level 24 h after levosimendan therapy. We also observed a significant correlation between LVEF and serum BNP level. For this reason, we suggest that the favourable effect of le-

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before levosimendan therapy</th>
<th>After levosimendan therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP [pg/mL]</td>
<td>5,305.97 ± 6,616.51</td>
<td>2,149.7 ± 3,029.87</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.5 ± 0.4</td>
<td>2.3 ± 0.5</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Conventional echocardiography</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LVEF [%]</td>
<td>35 ± 7</td>
<td>40 ± 6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RVEDD (cm)</td>
<td>2.68 ± 7.58</td>
<td>2.77 ± 5.41</td>
<td>0.433</td>
</tr>
<tr>
<td>RVESD (cm)</td>
<td>1.66 ± 5.80</td>
<td>1.66 ± 5.09</td>
<td>0.954</td>
</tr>
<tr>
<td>RVOTSF [%]</td>
<td>63.1 ± 8.09</td>
<td>63.23 ± 7.58</td>
<td>0.915</td>
</tr>
<tr>
<td>TAPSE (cm)</td>
<td>0.38 ± 0.12</td>
<td>0.41 ± 0.09</td>
<td>0.208</td>
</tr>
<tr>
<td>PAT (ms)</td>
<td>105.10 ± 13.96</td>
<td>110.77 ± 25.37</td>
<td>0.161</td>
</tr>
<tr>
<td>SPAP [mm Hg]</td>
<td>50 ± 10</td>
<td>42 ± 11</td>
<td>0.0001</td>
</tr>
<tr>
<td>RV E (m/s)</td>
<td>0.49 ± 0.13</td>
<td>0.54 ± 0.14</td>
<td>0.056</td>
</tr>
<tr>
<td>RV A (m/s)</td>
<td>0.48 ± 0.14</td>
<td>0.46 ± 0.12</td>
<td>0.457</td>
</tr>
<tr>
<td>RV E/A</td>
<td>1.12 ± 0.52</td>
<td>1.24 ± 0.46</td>
<td>0.255</td>
</tr>
<tr>
<td>RV ET (ms)</td>
<td>258.80 ± 47.79</td>
<td>247.60 ± 30.99</td>
<td>0.275</td>
</tr>
<tr>
<td>RV IVRT (ms)</td>
<td>91.57 ± 19.94</td>
<td>91.77 ± 17.83</td>
<td>0.960</td>
</tr>
<tr>
<td>RV IVCT (ms)</td>
<td>64.23 ± 17.42</td>
<td>68.00 ± 18.42</td>
<td>0.360</td>
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<tr>
<td>RV MPI (ms)</td>
<td>0.61 ± 0.15</td>
<td>0.40 ± 0.12</td>
<td>0.0001</td>
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<tr>
<td>Tissue Doppler echocardiography</td>
<td></td>
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<tr>
<td>RV S (m/s)</td>
<td>0.10 ± 0.05</td>
<td>0.12 ± 0.05</td>
<td>0.065</td>
</tr>
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<td>RV IVV (m/s)</td>
<td>0.08 ± 0.04</td>
<td>0.12 ± 0.05</td>
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<tr>
<td>RV IVA (m/s²)</td>
<td>1.89 ± 0.67</td>
<td>2.91 ± 1.39</td>
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</tr>
<tr>
<td>RV E’ (m/s)</td>
<td>0.09 ± 0.04</td>
<td>0.10 ± 0.08</td>
<td>0.070</td>
</tr>
<tr>
<td>RV A’ (m/s)</td>
<td>0.12 ± 0.06</td>
<td>0.12 ± 0.06</td>
<td>0.451</td>
</tr>
<tr>
<td>RV E’/A’</td>
<td>1.18 ± 1.53</td>
<td>1.37 ± 1.77</td>
<td>0.563</td>
</tr>
<tr>
<td>RV E'/E'</td>
<td>6.58 ± 2.88</td>
<td>7.50 ± 5.11</td>
<td>0.209</td>
</tr>
</tbody>
</table>

**Table 2.** The effect of levosimendan therapy on right ventricular functions and BNP

BNP — B-type natriuretic peptide; NYHA — New York Heart Association; LVEF — left ventricular ejection fraction; RVOTSF — right ventricular outflow tract shortening fraction; TAPSE — tricuspid annular plane systolic excursion; PAT — pulmonary flow acceleration time; SPAP — systolic pulmonary artery pressure; RV — right ventricle; E — early diastolic velocity; A — late diastolic velocity; ET — ejection time; IVRT — isovolumic relaxation time; IVCT — isovolumic contraction time; MPI — myocardial performance index; IVA — isovolumic acceleration; IVV — isovolumic velocity; E’ — flow velocity of the early diastole using tissue Doppler echocardiography; A’ — flow velocity of the late diastole using tissue Doppler echocardiography; S — peak systolic velocity of the myocardium at the very beginning of the isovolumic contraction period [21]. In our study, we suggest that IVA may be used as a noninvasive parameter for the assessment of the effect of levosimendan therapy on RV systolic functions in patients with ischaemic HF. IVA also showed a significant increase after the treatment. Additionally, TDI-derived Tei index decreased significantly, marking an improvement in global RV function. Duygu et al. [22] and Kasıkcıoğlu et al. [23] demonstrated that levosimendan therapy significantly improves RV systolic function, based on TDI-derived systolic indices.
Levosimendan therapy on neurohormonal modulation cannot be ignored, based on our findings. Supporting the results of our study, Farmakis et al. [25] revealed that the reduction of BNP after levosimendan therapy is an independent predictor of six month outcome in patients with advanced HF. Similarly, in a recent study performed by Lunghetti et al. [26], a significant decrease in serum pro-BNP level was obtained after levosimendan therapy.

Consequently, we demonstrated that levosimendan improves RV systolic function significantly, based on TDI-derived systolic indices. To the best of our knowledge, our study is the first to have investigated the impact of levosimendan therapy on RV systolic function, using the novel index IVA. We suggest that IVA is a non-invasive parameter which can be used for the determination of RV systolic function. We assume that patients with acute decompensated left HF can benefit from levosimendan therapy.

Strengths and limitations of the study
The strength of our study is a detailed evaluation of the effect of levosimendan therapy on RV systolic function, based on TDI-derived parameters. The major limitation is the small group size of our patients. Additionally, evaluating RV systolic function invasively, as an alternative way to the echocardiographic examination, would provide more valuable data. In order to determine the absolute benefit of levosimendan therapy, larger, randomised clinical trials are warranted.

CONCLUSIONS
Levosimendan improves RV systolic function as expressed by TDI-derived parameters in patients with acute decompensated HF.

Conflict of interest: none declared

References
7. Lang RM, Bierig M, Devereux RB. Recommendations for chamber quantification a report from the American Society of Echocardiography’s guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr, 2005; 18: 1440–1463.
Wpływ lewosimendanu na czynność prawej komory oceniany na podstawie wskaźników mierzonych metodą tkankowej echokardiografii doplerowskiej u chorych z niedokrwienią niewydolnością lewej komory

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Streszczenie

Wstęp: Dysfunkcja prawej komory (RV) jest powikłaniem zaawansowanej lewokomorowej (LV) niewydolności serca (HF) i wiąże się ze złym rokowaniem. Lewosimendan to lek o działaniu inotropowym dodatnim, który u chorych z HF poprawia kurczliwość serca, nie zwiększając zużycia tlenu przez miokardium.

Cel: Celem niniejszej pracy była ocena wpływu leczenia lewosimendanem na czynność skurczową RV u chorych z niedokrwienią HF na podstawie badania z zastosowaniem doplera tkankowego (TDI).

Metody: W badaniu uczestniczyło 30 chorych z HF hospitalizowanych w ośrodku autorów z powodu pojawienia się objawów niewyrównanej HF, u których frakcja wyrzutowa LV wynosiła poniżej 40% i których zakwalifikowano do III–IV klasy czynnościowej wg New York Heart Association (NYHA). Za pomocą TDI zmierzono prędkości pierścienia zastawki trójdzielnej w czasie skurczu [akceleracja (IVA) i maksymalna prędkość miokardium w czasie skurczu izowolumetrycznego (IVV) oraz maksymalna prędkość miokardium w czasie fazy wyrzutowej (Sa)] i wskaźniki czynności rozkurczowej [prędkości wczesno- (Ea) i późnorozkurczowe (Aa), współczynniki Ea/Aa i E/Ea oraz wskaźnik Tei]. Wszystkie pomiary powtórzono 72 h po przyjęciu leku.

Wyniki: Po zakończeniu leczenia oceniane za pomocą TDI wskaźniki czynności skurczowej RV, IVA i IVV istotnie się zwiększyły, natomiast wartość wskaźnika Tei zmniejszyła się. Ponadto stwierdzono istotne obniżenie stężenia peptydu natruptycznego typu B w surowicy. Nie zaobserwowano istotnych zmian we wskaźnikach czynności rozkurczowej RV ocenianych za pomocą TDI.

Wnioski: U pacjentów z ostrą niewyrównaną HF lewosimendan poprawia czynność skurczową RV ocenianą na podstawie parametrów mierzonych metodą TDI.

Słowa kluczowe: lewosimendan, niedokrwieniata niewydolność serca, prawa komora, dopler tkankowy

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