The Role of Levosimendan Infusion in Improving Renal Function in Worsening Type II Cardio-Renal Syndrome

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ABSTRACT

The cardio-renal syndrome (CRS) includes a variety of pathologic conditions (acute or chronic) where the primary failing organ can be either the heart or the kidney. We present three cases of heart failure (HF) patients hospitalized for acute decompensation, who presented a CRS type II rapidly worsening after high doses of furosemide infusion.

METHODS: From June 2015 to March 2016 all patients admitted to our Department for chronic refractory heart failure (NYHA class IV), underwent a determination of BNP and other laboratory tests (creatinine, GFR, haemoglobin), echocardiogram, non-invasive cardiac output measurement and 6 min walking test. Patients underwent a single infusion of levosimendan in case of CRS type II, at 0.1 µg/kg/min for 24-36 hours. Clinical / laboratory evaluation was repeated 24 hours and 1 week after infusion of the drug.

RESULTS: Patients treated with levosimendan allowed the reduction of loop diuretics dose, because of the restoration of renal function. Body weight and peripheral edema were progressively reduced, and cardiac output improved. At discharge, exercise capacity significantly improved, functional class proved to be in NYHA class II-III, renal function and neurohormonal assessment (BNP) ameliorated. At one-month follow-up the clinical conditions remained stable as well as the parameters of renal function and plasma BNP.

CONCLUSION: This clinical experience demonstrated that one of most frequent and dangerous evolution of renal impairment (development of Acute Kidney Injury) might be improved by using a single dose of levosimendan, which has a proved effect in improving cardiac function and urine output. (Int J Biomed Sci 2018; 14 (2): 78-84)

Keywords: congestive heart failure; cardio-renal syndrome; levosimendan; worsening heart failure
INTRODUCTION

The cardio-renal syndrome (CRS) includes a variety of pathologic conditions (acute or chronic) where the primary failing organ can be either the heart or the kidney. The classification of CRS into five different subtypes (1) allows clinicians to fully characterize the pathophysiologic interactions of the combined heart/kidney disorder. In particular, the type II CRS has been characterized by chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive and permanent chronic kidney disease. This subtype refers to a more chronic state of kidney disease that usually complicated a chronic heart failure. Both hypertension and hypotension may determine CRS, but for the prevention of CRS type II the optimal management of sodium and extracellular fluid volume through low-sodium intake and diuretics seems to be crucial. Those patients who require the highest doses of loop diuretics have the highest probability of CRS and mortality, according to a further activation of neurohumoral pathways and worsening renal function (2, 3). Levosimendan is an effective therapeutic option in acute advanced HF in order to improve hemodynamics and tissue perfusion (4), relieve symptoms of congestion and fatigue (5) and augment renal blood flow and glomerular filtration rate (GFR) through afferent arteriolar dilatation and increase urine production (6, 7).

We present three clinical cases of chronic congestive heart failure (CHF) patients admitted for acute decompensation (ADHF) with pre-existing (according to the value of GFR at admission) CRS type II who rapidly worsened (acute kidney injury, AKI) after administration of high dose of furosemide due to fluid overload, and evaluate the efficacy of a single levosimendan infusion in improving renal function.

PATIENTS AND METHODS

From June 2015 to March 2016, all patients admitted to our Department for chronic refractory systolic heart failure were requested to enter the study. Systolic HF patients admitted for acute decompensation and fluid overload (CHF) who developed AKI during loop-diuretic infusion administered for reducing fluid amount, underwent a single dose of levosimendan infusion and entered in this clinical observational experience. Patients were classified as having CHF according to the criteria commonly accepted in literature (8), namely the presence of 2 major criteria or 1 major criterion + 2 minor criteria according to the Framingham score, and a NYHA functional class II, III, or IV, due to an exacerbation of symptoms with at least 1 class deterioration. The presence of inadequate echo images, severe renal impairment (glomerular filtrate<30 ml/min/m²) or no adherence to therapy and disagreement with the periodical follow-up, were considered exclusion criteria. All patients underwent a clinical examination, a 12-lead electrocardiogram, plasma determination of brain natriuretic peptide (BNP) and other laboratory’s tests (creatinine, haemoglobin, water composition (on admission and at discharge), 6-minute walk test (6MWT), non-invasive cardiac output (CO) and a transthoracic echocardiogram within 48 hours upon hospital discharge. All patients were treated with high dose of furosemide and water restriction patients who developed CRS type II (creatinine rapidly deteriorating without any change in clinical symptoms and persistence of fluid overload) the infusion of a single dose of levosimendan was considered (at the dosage of 0.1 µg/kg/min for 24-36 hours, as per summary of product characteristics). After 24 h and 1 week following the infusion, patients underwent a clinical examination, non-invasive CO measurement, 6MWT, transthoracic echocardiography, 12-lead electrocardiogram and laboratory tests. Clinical follow-up was obtained after 6-month.

• BNP was measured after collecting blood sample by venipuncture and immediately analysed with the bedside Triage B type natriuretic fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). The Triage Meter is used to measure BNP concentration by detecting a fluorescent emission that reproduces the amount of BNP in the blood. Then, the Triage Meter measured the fluorescent intensity of the BNP assay area. The assay results were completed in 15 minutes.

• Echocardiograms were performed with a GE Vivid 7 Pro, according to the recommendations of the American Society of Echocardiography (9). Two-dimensional apical 2- and 4-chamber views were used for volumetric measurements; LVEF was calculated with a modified Simpson’s method using biplane apical (2- and 4-chamber) views. The LV end-diastolic volume and end-systolic volumes were recorded. All the echo examinations were performed by expert operators blinded to the results of BNP assay; the intra-observer variability in the evaluation of LVEF was <5%. Echocardiographic measurements included LV end-diastolic diameter and diastolic thickness of the ventricular septum and posterior LV wall. Left ventricular systolic dysfunction was defined as an LVEF <50%. Diastolic dysfunction was graded according to a predefined modification of classifications already used.
1) **Impaired relaxation**: early filling wave (E) / atrial filling wave (A) ratio (E/A) < 1 and deceleration time (DT) > 220 msec in subjects aged < 55 years or E/A < 0.8 and DT > 220 msec in subjects aged > 55 years; systolic wave (S) / diastolic wave (D) ratio of pulmonary veins (PV) (PV S/D) > 1, and atrial reversal flow velocity (AR) < 35 cm/sec;

2) **pseudonormal**: E/A 1 to 2, DT 150 to 220 msec, PV S/D ratio < 1, and AR > 35 cm/sec;

3) **restrictive**: E/A > 2, DT < 150 msec, S/D ratio < 1, and AR > 35 cm/sec).

In patients suffering from atrial fibrillation at the time of the echocardiogram, the diastolic function was classified as: 1) restrictive pattern (DT <150 msec) or 2) indeterminate (DT >150 msec). The pulmonary artery pressure (PAP) was obtained by determining the peak velocity of the tricuspid regurgitation jet, plus 5 or 10 mmHg for right atrial pressure according to right atrial size, severity of regurgitation and appearance of the inferior vena cava. From Doppler tissue imaging of the annulus, the E’ wave (early annular velocity opposes in direction to the mitral inflow) was determined and the ratio E/E’ calculated. Right ventricular function was investigated by M-mode echocardiography, obtaining the tricuspid annular plane systolic excursion (TAPSE) (10). The medical therapy was normally assumed before the echocardiogram and the BNP measurements were obtained before the echo examination.

- **Non-invasive cardiac output measurement.** For the measurement of non-invasive cardiac output (CO), an inert gas rebreathing method (Innocor, Innovison A/S, Odense, Denmark) was used. The system utilized a N$_2$O (blood soluble gas) and SF$_6$ (blood insoluble gas) enriched with O$_2$ of 0.5% and 0.1% respectively. Tidal volume was progressively increased in the closed circuit to match the physiologic increase. Use the SF$_6$ allowed measuring the volume of lungs, valve and rebreathing bag. N$_2$O concentration decreases during the rebreathing manoeuvre, with a rate proportional to pulmonary blood flow. In the absence of pulmonary shunt, pulmonary blood flow equals CO. This method was proved to be closely correlated with thermodilution (R=0.93) and the direct Fick method (R=0.94) (11) and it demonstrated to be a robust prognostic method in CHF discharged patients (12).

- **Six-minute Walk Test (6MWT)** was performed in the discharging day according to the ATS Statement of the American Thoracic Society (13). CHF patients able to walk underwent 6MWT if did not meet the exclusion criteria (unstable angina and myocardial infarction during the previous month, resting heart rate >120 beats/min; systolic blood pressure>180 mmHg or diastolic blood pressure>100 mmHg).

**RESULTS**

Three consecutive male patients (mean 78 years) with severe systolic HF (mean LVEF 15.6 ± 0.94%), admitted for acute decompensation who developed CRS type 2, were treated with a single dose of levosimendan. Three HF patients were excluded because of a severe deterioration of glomerular filtrate (<30 ml/min/1.73 m$^2$), and one for the presence of diastolic HF.

Their clinical characteristics are briefly summarized below:

1) 83 year-old man with a long history of systolic HF due to rheumatic valvular heart disease was admitted to our hospital for acute decompensation (ADHF) characterized by shortness of breath (NYHA IV) at rest, edema up to the root of legs and symptoms of congestive heart failure. On chest radiography, right pleural effusion and suspect of left pneumonia emerged. During hospitalization the patient was treated with high-dose parenteral loop diuretics (500 mg/die) and water restriction (maximum 1 L/day orally) and cycle of antibiotic therapy with little benefit in weight change and dyspnoea. He remained in class NYHA IV.

2) 82 year-old man with a long history of systolic HF due to ischemic and valvular cardiomyopathy was admitted to our hospital for ADHF characterized by shortness of breath at rest (NYHA IV) and symptoms of congestive heart failure. During hospitalization the patient was treated with high-dose parenteral loop diuretics (furosemide 200 mg/die), and water restriction (maximum 1 L/day orally) with little benefit in weight change and dyspnoea that remained at rest.

3) 70 year-old man with a long history of systolic HF due to idiopathic cardiomyopathy was admitted to our hospital for ADHF characterized by shortness of breath (NYHA IV) and symptoms of fluid overload.

During hospitalization the patient was treated with high-dose parenteral loop diuretics (furosemide 500 mg/day, venous vasodilators (nitroprusside) and water restriction (maximum 1 L/day orally) with little benefit in weight reduction and dyspnoea but he remained in NYHA class IV.

Unfortunately, not all those HF patients improved after an adequate, high iv dose of furosemide, demonstrating a clear resistance to loop diuretics. In all patients a worsening renal failure in a chronic cardio-renal syndrome type
2 (according to the admission GFR) was diagnosed, developing with hypotension and progressive worsening of renal and cardio-circulatory function. They were treated with a discontinuation of vasodilator, reducing the infusion of loop diuretics and beginning an infusion of levosimendan i.v at the dose of 0.1 µg/kg/min in continuous infusion without a starting bolus.

Per protocol levosimendan loading dose should not be administered, starting the infusion at the dosage of 0.1 µg/kg/min for 24-36 hours in order to reach the dosage of 12.5 mg. Reduction of systolic blood pressure<80 mmHg, tachycardia with heart rate>140 beats/min, and symptomatic hypotension are considered criteria for reducing the dosage of levosimendan, or suspending the infusion for 30-60 min until the dose-limiting event resolves. The therapy prescribed in these patients included angiotensin converting enzyme inhibitors (enalapril, ramipril), angiotensin receptor blockers (candesartan, losartan) in case of enalapril/ramipril intolerance, beta-blocker (bisoprolol) and spironolactone at low dose. These therapies were maintained during treatment.

Before the infusion of levosimendan/furosemide, within 6 hours after ending the infusion, and at 1-week follow-up, all the parameters scheduled were measured. In all patients a non-invasive measurements of non-invasive CO during the infusion (between 12 and 24 hour) was obtained, as described previously. Levosimendan infusion lasted 24-36 hours and was well tolerated in all patients.

In the following days we observed a recovery of abundant diuresis with a progressive reduction in body weight and peripheral edema, as well as improvement of renal and of cardiac output (CO) (Table 1).

At the time of discharge the exercise capacity of each patient significantly improved, corresponding to NYHA class II-III, renal function and neurohormonal asset (BNP) improved even one-week after administration of levosimendan. At one-month follow-up the clinical conditions of all patients were stable, as were the parameters of renal function and the neurohormonal asset (plasma BNP). At six-month follow-up one patient (SL) died a cardiac death (cardiogenic shock).

### Table 1. Main patients’ clinical/functional parameters during hospitalization

<table>
<thead>
<tr>
<th></th>
<th>S.L. baseline</th>
<th>S.L. end-infusion</th>
<th>S.L. 1-week follow-up</th>
<th>R.S. baseline</th>
<th>R.S. end-infusion</th>
<th>R.S. 1-week follow-up</th>
<th>B.M. baseline</th>
<th>B.M. end-infusion</th>
<th>B.M. 1-week follow-up</th>
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<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>2,1</td>
<td>2</td>
<td>1,9</td>
<td>2,32</td>
<td>2,4</td>
<td>2</td>
<td>1,8</td>
<td>1,29</td>
<td>1,24</td>
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<tr>
<td>GFR (ml/min/1.73 m²)</td>
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<td>34</td>
<td>38</td>
<td>36</td>
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<td>38</td>
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<td>Weight (kg)</td>
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<td>85</td>
<td>76,6</td>
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<td>Sodium (mmol/l)</td>
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<td>Potassium (mmol/l)</td>
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<td>4</td>
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<td>3,5</td>
<td>3,9</td>
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<td>2100</td>
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<td>1500</td>
<td>2300</td>
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<td>BNP (pg/ml)</td>
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<td>840</td>
<td>1008</td>
<td>2082</td>
<td>2630</td>
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<td>CO (l/min)</td>
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<td>2,5</td>
<td>4,8</td>
<td>4,6</td>
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<td>3,2</td>
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<tr>
<td>CI (l/min/m²)</td>
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<td>2,4</td>
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<td>2,4</td>
<td>2,4</td>
<td>1,73</td>
<td>2,06</td>
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<td>LVEF (%)</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>17</td>
<td>29</td>
<td>25</td>
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<td>PAP (mmHg)</td>
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<tr>
<td>TAPSE (mm)</td>
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<td>18</td>
<td>11</td>
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<td>15</td>
<td>15</td>
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<td>6MWT (m)</td>
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<td>50</td>
<td>80</td>
<td>120</td>
<td>40</td>
<td>60</td>
<td>125</td>
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</tbody>
</table>

GFR, glomerular filtration rate; CO, non-invasive cardiac output; BNP, brain natriuretic peptide; 6MWT, 6 Minute Walking Test; CI, non-invasive cardiac index; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; NYHA, New York Heart Association.
DISCUSSION

The mortality rate of HF patients admitted for acute decompensation was described in the large ADHERE registry (14), in which creatinine plasma level $\geq 2.75$ mg/dl, BUN $\geq 43$ mg/dl and systolic blood pressure $<115$ mmHg identified a high-risk in-hospital mortality subgroup (mortality rate 23.8%). In-hospital mortality seemed to be higher in chronic HF patients than in de-novo HF subjects, and this aspect was justified by the association with important co-morbidities (diabetes mellitus, chronic bronchitis), older age and pronounced renal failure (15). In the experience of Davison et al. (16), worsening heart failure (WHF) during the first 5 days of admission for ADHF occurred in approximately 10% to 15% of patients and was associated with longer length of stay and an increased risk of 60-day cardiovascular death or re-hospitalization, doubling the risk of 180-day mortality. The strongest predictor of WHF in the pooled database was renal function (creatinine, BUN). Creatinine and BUN should be considered a marker of renal dysfunction and hypoperfusion but may also reflect neurohormonal activation in HF (17).

The clinical response to loop diuretics, administrated to reduce fluid overload, seems to be different according to the concept of ‘diuretic resistance’, and the degree of response to diuretic allowed to stratify different outcomes (18). In the experience of Cheng et al. (19), the quote of HF patients who did not respond to loop diuretics experienced an increase of plasma BNP and had a worse prognosis in comparison with patients with a clear reduction of plasma BNP. Butler et al. (20) described three major adverse trajectories for in-hospital course of the patient admitted for ADHF:

Trajectory 1. Patients with a downward course with worsening heart failure from admission onwards.

Trajectory 2. Patients initially improving during hospitalization but whom subsequently deteriorate requiring intensification of therapy.

Trajectory 3. Patients who remain refractory to therapy despite further intensification.

On the other hand, the loop diuretics in acute HF patients treated for the fluid overload might induce a deterioration of renal function, classically defined as a $\geq 0.3$ mg/dl increase in serum creatinine or $\geq 25\%$ decrease in the estimated glomerular filtration rate from the baseline value. Very recently, Sokolski et al. (21), differentiate a ‘true worsening renal function’ (WRF) characterized by the decreasing of renal function plus the presence of deterioration/no improvement in clinical status from a ‘pseudo-WRF’ in which only a biochemical deterioration emerged. They observed, in 132 acute HF patients, that a ‘true-WRF’ developed in 10% of the population treated with diuretics in comparison with 11% in which a ‘pseudo-WRF’ were scheduled.

In the present report we present a population of patients in the third trajectory, in whom no clinical/biochemical improvements were noted and inotropic therapy should be started despite incremental doses of diuretics. Moreover, the refractoriness to diuretic therapy seemed to be due to a deterioration of renal function and therefore a CRS type II was diagnosed.

In our previous experience, levosimendan infusion during an ADHF episode improved the NYHA class, with BNP decreased, improved the meters of the 6-min walking test travelled by each patient, and improved LVEF, with positive effects persisting over one week after the infusion (22). In this study, plasma BNP was significantly reduced (Table 1) while our echocardiographic parameters did point out significant differences in LVEF, left ventricular volumes, diastolic function, pulmonary pressure and TAPSE both at the end of levosimendan infusion and at 1-week follow-up after levosimendan administration.

Renal dysfunction observed after the high-dose of loop diuretics in our 3 HF patients depicted an acute kidney injury in a CRS type II that is a common clinical features when treating chronic, congestive HF. The infusion of levosimendan permitted the reduction of furosemide dosage, the improvement of haemodynamic parameters and a partial recovery of renal function. Moreover, the sensitive improvement in cardiac output evaluated with a non-invasive rebreathing method demonstrated the positive inotropic effect of levosimendan in these specific cases.

It is well documented that serum creatinine, urea nitrogen and BNP are strong and independent prognostic parameters in CHF patients. In the experience of Žemljic et al. (23), based on 20 CHF patients awaiting cardiac transplantation, a single levosimendan administration determined a significant improvement of plasma creatinine and creatinine clearance (p=0.005) at 3-month follow-up. The renoprotective effect of the drug might be related to an increase of renal medullar blood flow in spite of a reduction of the cortical flow (24), or to a change of inflammatory status (reduction of interleukin-6) (25). This favorable effect might be considered as a resource for anti-inflammatory therapy. Recently, Fedele et al. (26) using an intravascular renal artery Doppler examination in 21 HF patients, demonstrated the significant effect of levosimendan in improving renal blood flow and GFR through a vasodilation of the
renal artery with an amelioration of serum level of BUN and creatinine.

In a group of 14 systolic HF patients with worsening renal failure, Zorlu et al. (27) observed that levosimendan infusion increased significantly the GFR and creatinine plasma level, improving the echocardiographic left ventricular functions as well.

Traditionally, the reduced renal perfusion according to the deterioration of CO has been considered the most important cause of renal impairment in acute decompensated HF. In addition to renal hypoperfusion, secondary to pump failure and redistribution of blood flow to vital organs (brain, etc.), intrarenal vasoconstriction and venous congestion may play a role in worsening renal function. However, according to the results of the LIDO trial (28), in which levosimendan infusion improved renal function (mean change in creatinine concentration -0.10 mg/dl) while dobutamine did not, the simple inotropic effect might not explain the amelioration of renal parameters. In the REVIVE trials, levosimendan reduced the incidence of ADHF episodes as compared with placebo; however, this was not associated with improved survival (29).

In conclusion, we observed that one of most frequent and dangerous evolution of CHF (development of AKI in CRS type II in patients treated with high doses of loop diuretics) might be counterbalanced by a single administration of levosimendan infusion, which might determine an improvement of medullar renal flow and of cardiac output in order to increase diuresis restoring renal function.

REFERENCES

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