

# Haemodynamic effects of levosimendan in advanced but stable chronic heart failure

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## Abstract

**Aims** Levosimendan improves haemodynamics in acute decompensated heart failure (HF). However, it is increasingly used for repetitive or intermittent infusions in advanced but stable chronic HF, without clear indication, selection criteria, or effect. We tested the hypotheses that (1) levosimendan improves haemodynamics in stable chronic HF and (2) that the response is dependent on baseline clinical and haemodynamic factors.

**Methods and results** Twenty-three patients [median age 56 (49–64) years, four (17%) women] with stable New York Heart Association (NYHA) III and IV HF received a single 24 h levosimendan infusion. Non-invasive haemodynamics (inert gas re-breathing technique), estimated glomerular filtration rate, and N-terminal pro-brain natriuretic peptide were assessed before and after infusion. Levosimendan had the following effects (median change): a significant increase in cardiac output (+9.8 ± 21.6%;  $P = 0.026$ ) and decrease in N-terminal pro-brain natriuretic peptide (−28.1 ± 16.3%,  $P < 0.001$ ), estimated total peripheral resistance (−16.9 ± 18.3%,  $P = 0.005$ ), and mean arterial pressure (−5.9 ± 8.2%,  $P = 0.007$ ), but no change in estimated glomerular filtration rate (+0.89 ± 14.0%,  $P = 0.955$ ). There were no significant associations between baseline clinical and/or haemodynamic factors and the levosimendan effect on cardiac output.

**Conclusions** Levosimendan was associated with improved haemodynamics in patients with stable chronic HF, but we could not identify any predictors of the magnitude of haemodynamic response.

**Keywords** Heart failure; Repetitive treatment; Inotrope; Inodilator; Levosimendan; Cardiac output

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## Introduction

Heart failure (HF) has a prevalence and incidence rates of 2–3% and 0.5%, respectively, and is associated with severely compromised quality of life, poor prognosis, and high costs to society.<sup>1,2</sup> Acute decompensated HF (ADHF) is the most common cause of hospitalization,<sup>3</sup> and cardiogenic shock occurs in about 4% of ADHF admissions.<sup>4</sup> Conventional inotropes improve haemodynamics and organ perfusion and relieve symptoms, but due to short half-lives, they are limited to selected inpatients and outpatients with continuous infusions and are pro-ischaemic, are pro-arrhythmic, and may be associated with increased mortality.<sup>5–9</sup>

Levosimendan is an intravenous inodilator agent whose inotropic effect is mediated primarily by calcium

sensitization, without concomitant increase in intracellular calcium levels or myocardial metabolic demand.<sup>10,11</sup> In early studies in ADHF, levosimendan improved haemodynamics and mortality compared with dobutamine<sup>12</sup> and placebo.<sup>13</sup> In later studies, it was not superior to dobutamine,<sup>14</sup> and it improved symptoms but increased hypotension and arrhythmia compared with placebo.<sup>15</sup>

Advanced but stable chronic HF affects up to 5% of the HF population and is characterized by a low-output state, severe symptoms, frequent hospitalizations, and high mortality.<sup>5,16</sup> Continuous outpatient conventional inotrope infusions may be required to keep patients out of hospital and to preserve perfusion and end organ function, for example, in patients awaiting heart transplantation, especially those who may not be suitable for bridging with left ventricular assist device

(LVAD). However, this practice is still controversial and may be associated with increased mortality.<sup>17–19</sup>

Levosimendan has an active metabolite that peaks 80–90 h after administration, and the beneficial haemodynamic effects are sustained for at least 7 days.<sup>20</sup> This has led to a growing but highly variable practice of intermittent (as needed) or repetitive (planned) treatment in advanced but stable HF.<sup>21</sup> This may be beneficial in select patients.<sup>19,22</sup> The LevoRep trial did show improved 6 min walking capacity and improved Kansas City Cardiomyopathy Questionnaire but did not meet the high primary endpoint criteria; however, effects on secondary endpoints were promising.<sup>23</sup> The LION-HEART trial showed lower N-terminal pro-brain natriuretic peptide (NT-pro-BNP) area under the curve and the secondary endpoints HF hospitalization and combined HF hospitalization and death.<sup>24</sup> However, confirmatory trials are needed, and in particular, improved selection of patients most likely to respond and derive benefit is needed. Therefore, we tested the hypotheses that (1) levosimendan improves haemodynamics also in stable chronic HF and (2) that the response is dependent on baseline clinical and/or haemodynamic factors.

## Methods

### Study population

This was a prospective single-centre single-arm trial of adult patients with advanced but stable chronic HF with New York Heart Association class (NYHA) III and IV symptoms and an ejection fraction (EF) of <40%, who were scheduled for elective intravenous levosimendan infusion based on consensus clinical indication at the Karolinska University Hospital. Patients were either listed for or undergoing evaluation for heart transplantation, LVAD, or palliative care. Patients were excluded if they were unable or unwilling to participate in the study protocol.

The study protocol conformed to the Declaration of Helsinki and received approval from the regional ethical review board. Written informed consent has been obtained from all patients.

### Intervention: levosimendan infusion

All patients reported to the hospital ward in the morning and received a single 24 h levosimendan infusion initially at a rate of 0.1 µg/kg/min without bolus. If the patient tolerated the initial dosage and based on clinical judgment, we gradually increased the infusion rate to 0.2 µg/kg/min. The infusions were maintained at a constant rate for 24 h, unless symptomatic hypotension, defined as systolic blood pressure below 80 mmHg, occurred or the patient had a major cardiovascular

event like arrhythmia. In case of hypotension or a major cardiovascular event, the infusion was stopped for 30–60 min or until the dose-limiting event had resolved and then restarted at half the rate being received at the time of the untoward reaction.

### Data collection and analysis

Prior to and immediately after the 24 h infusion, physical examination and non-invasive haemodynamic evaluation were performed using an inert gas re-breathing method (Innocor® Innovision A/S, Denmark), and plasma samples for creatinine and NT-pro-BNP were collected. The Innocor is an established, safe, and non-invasive technique for assessing pulmonary blood flow (PBF) and cardiac output (CO). It uses a gas mixture that contains two inert compounds in a closed re-breathing system; one compound is blood soluble (N<sub>2</sub>O), whereas the other is insoluble (SF<sub>6</sub>). The soluble gas dissolves in the blood of the pulmonary capillaries and is subsequently washed out by the blood perfusing the lungs. Therefore, the disappearance rate of N<sub>2</sub>O from expired air is directly proportional to the PBF, which in turn equals CO in the absence of significant shunting. Thus, we report PBF, but for purposes of discussion, refer to changes in CO. This technique has been validated against invasive measurements of CO in HF patients (direct Fick, thermodilution, and dye dilution) and is safe and accurate in different clinical settings.<sup>25–27</sup>

Estimated total peripheral resistance (eTPR) was calculated using the formula  $eTPR = [\text{mean arterial pressure (MAP)} - \text{central venous pressure}] / \text{CO} \times 80$  and was simplified by assuming that central venous pressure was 15. The estimated glomerular filtration rate was determined using the chronic kidney disease epidemiology collaboration formula.<sup>26</sup>

### Statistical analysis

Statistical analysis was performed using SPSS Version 22.0 (SPSS Inc., Chicago, IL, USA). All continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and expressed as median (interquartile range), while categorical variables were expressed as *n* and percentages. Significant testing between continuous variables was subsequently performed using the Mann–Whitney U test (skewed variables). Similarly, Wilcoxon's paired test (skewed data) was used to compare median values before and after each infusion. Association between baseline clinical and haemodynamic factors and the outcome change in CO was analysed using Spearman's correlations. A two-sided *P* value of <0.05 was considered statistically significant.

## Results

We included 23 patients [median age 56 (49–64) years, four women (17%)] with median EF 20% (15–31%) and NYHA IIIA ( $n = 4$ , 17.4%), NYHA IIIB ( $n = 18$ , 78.3%), or NYHA IV ( $n = 1$ , 4.4%). Table 1 details the baseline characteristics. Median CO was 3.05 L/min (2.8–3.4), median NT-pro-BNP 3400 pg/mL (1882–6597), median MAP 79 mmHg (74–87), and median eTPR 1628 dyn·s/cm<sup>5</sup> (1405–2034). The target levosimendan dose was reached in all patients.

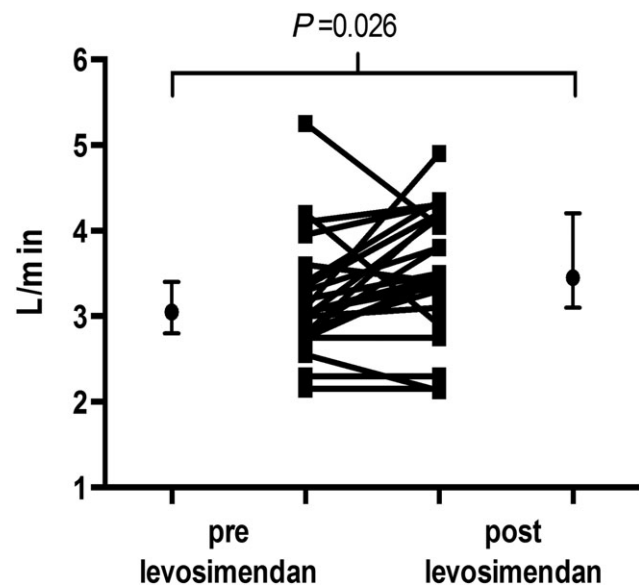
Figure 1 illustrates the effect of levosimendan on CO. Levosimendan infusion was associated with a significant increase in CO from 3.05 L/min (2.8–3.4) to 3.45 L/min (3.1–4.2), corresponding to a median change of  $+9.8 \pm 21.6\%$ ,  $P = 0.026$ .

Figure 2 shows the effect of a single 24 h levosimendan infusion on the remaining study variables. Levosimendan infusion caused a significant decrease in NT-pro-BNP from 3400 pg/mL (1882–6597) to 2530 pg/mL (1108–6410), corresponding to a median change of  $-28.1 \pm 16.3\%$ ,  $P < 0.001$ ; eGFR from 62 mL/min/m<sup>2</sup> (35–78) to 61 mL/min/m<sup>2</sup> (40–85), corresponding to a median change of  $-1.6 \pm 14.0\%$ ,  $P = 0.955$ .

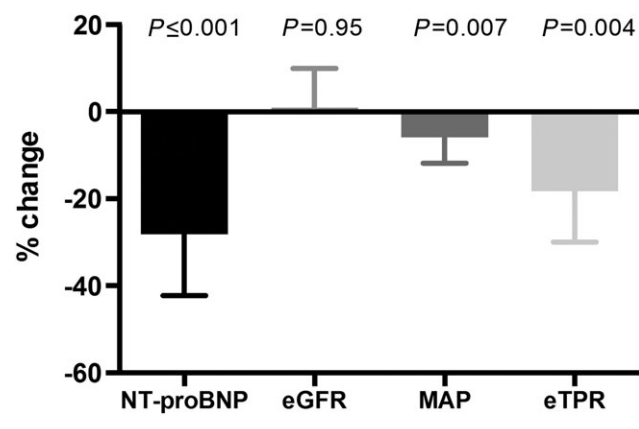
The levosimendan-associated increase in CO was due to an increased stroke volume from 48 mL/min (40–53) to 52 mL/min (46–61), corresponding to a median change of  $7.5 \pm 22.6\%$ ,  $P = 0.021$ , since heart rate was unchanged from

79 mmHg (74–87) to 74 mmHg (69–81) corresponding to a median change of  $5.9 \pm 8.2\%$ ,  $P = 0.007$ . The estimated glomerular filtration rate showed insignificant change from 62 mL/min/m<sup>2</sup> (35–78) to 61 mL/min/m<sup>2</sup> (40–85), corresponding to a median change  $0.89 \pm 14.0\%$ ,  $P = 0.955$ .

**Figure 1** Individual and median (interquartile range) cardiac output before and after levosimendan infusion.



**Figure 2** Effect of a single 24 h levosimendan infusion on N-terminal pro-brain natriuretic peptide (NT-pro-BNP), estimated glomerular filtration rate (eGFR), mean arterial pressure (MAP), and estimated total peripheral resistance (eTPR). Error bars represent median change and standard deviation.



**Table 1** Baseline characteristics

| Variable   |                  |
|--|------------------|
| <b>Demographics</b>                                    |                  |
| Age (years)  | 56 (49–64)       |
| Female gender (n/%)                                    | 4/17             |
| <b>Haemodynamics and heart failure characteristics</b> |                  |
| Heart rate (b.p.m.)                                    | 69 (61–73)       |
| Systolic blood pressure (mmHg)                         | 101 (98–105)     |
| Diastolic blood pressure (mmHg)                        | 68 (63–73)       |
| Mean blood pressure (mmHg)                             | 79 (74–87)       |
| Cardiac output (L/min)                                 | 3.1 (2.8–3.4)    |
| NT-pro-BNP (pg/mL)                                     | 3400 (1882–6597) |
| eGFR (mL/min/m <sup>2</sup> )                          | 62 (35–78)       |
| eTPR (dyn·s/cm <sup>5</sup> )                          | 1628 (1405–2034) |
| BSA (m <sup>2</sup> )                                  | 2.0 (1.9–2.2)    |
| EF (%)   | 20 (15–31)       |
| NYHA class: IIIA/IIIB/IV (n)                           | 4/18/1           |
| Sinus rhythm (n/%)                                     | 8/35             |
| Atrial fibrillation                                    | 15/65            |
| <b>Device therapy</b>                                  |                  |
| PM (n/%)   | 1/4              |
| ICD (n/%)  | 6/21             |
| CRT-P (n/%)  | 1/4              |
| CRT-D (n/%)  | 15/65            |
| <b>Medical therapy</b>                                 |                  |
| Beta-blockers (n/%)                                    | 22/95            |
| ACEI/ARB (n/%)   | 22/95            |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surface area; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; eTPR, estimated total peripheral resistance; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association functional classification; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; PM, pacemaker. Continuous variables are presented as median and interquartile range (Q1–Q3) and categorical variables as numbers (n) and percentages.

69 b.p.m. (62–74) to 70 b.p.m. (61–76), corresponding to a median change of  $0.67 \pm 6.5\%$ ,  $P = 0.159$ .

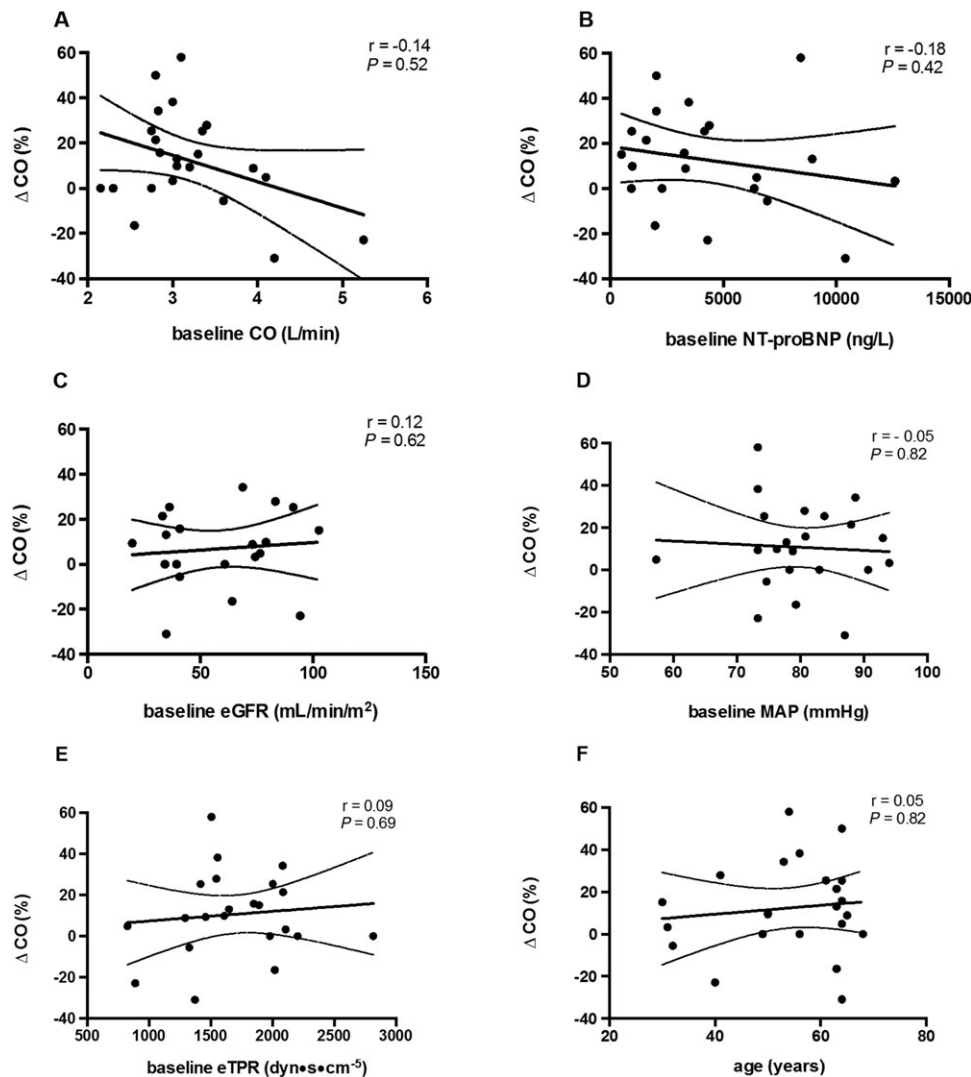
In correlations analyses, *Figure 3A–F* illustrates the correlation between baseline clinical/haemodynamic factors and the change in CO. We found no significant correlation between baseline characteristics or haemodynamic variables and the change in CO.

## Discussion

To our knowledge, this is the first study to show that levosimendan improves CO also in advanced but stable chronic HF. There are no previous data about the

levosimendan effect in patients with advanced but stable chronic HF; however, two previous studies have shown improvement in haemodynamic function measured by invasive haemodynamic monitoring in patients with decompensated HF.<sup>12,28</sup> Moreover, we confirmed findings from previous studies documenting that levosimendan also reduces NT-pro-BNP, MAP, and eTPR.<sup>29–31</sup> However, given that levosimendan is frequently used in stable HF despite a lack of convincing evidence or indications, we also examined whether baseline clinical and haemodynamic factors affected the response to levosimendan and observed no significant association between baseline clinical or haemodynamic parameters and levosimendan effect on CO.

**Figure 3** Correlations between baseline cardiac output (CO) (A), N-terminal pro-brain natriuretic peptide (NT-pro-BNP) (B), estimated glomerular filtration rate (eGFR) (C), mean arterial pressure (MAP) (D), estimated total peripheral resistance (eTPR) (E), and age (F) and change in cardiac output in response to levosimendan.



Levosimendan was first approved in Sweden in the year 2000 and subsequently throughout Europe, and the early LIDO<sup>12</sup> and RUSSLAN<sup>13</sup> trials were promising. However, the larger SURVIVE<sup>14</sup> and REVIVE<sup>15</sup> trials were not confirmatory, and levosimendan is not licensed in the USA. Early enthusiasm led to rapid adoption in Europe, and although European guidelines do not give preference among different inotropes,<sup>2</sup> in the Swedish Heart Failure Registry, levosimendan is the overwhelming inotropic agent of choice by cardiologists.<sup>21</sup> Furthermore, the ease of administration and long half-life allow administration to ambulatory patients in general cardiology wards or even as shortened infusions in office settings. Indeed, in Sweden between 2000 and 2011, the proportion of levosimendan treatments that were in stable patients ranged widely between 0% and 65% between different hospitals,<sup>21</sup> but it is unclear whether this practice is justified.

Several small observational and randomized studies were reviewed<sup>19</sup> and summarized<sup>30</sup> and recently updated<sup>22</sup> in meta-analysis and suggested that in selected patients, repetitive or intermittent levosimendan appears promising and may improve outcomes including mortality but selection criteria may need improvement. However, in SURVIVE, levosimendan was associated with borderline better 31 day survival compared with dobutamine in the majority of patients with a history of HF prior to the relevant ADHF episode (hazard ratio 0.52–1.03, *P* for interaction = 0.05), consistent with a potential benefit in stable patients with chronic HF. We studied a single use of levosimendan in advanced but stable chronic HF, which is different from repetitive or intermittent use; however, the patient population is similar as both of them have stable chronic HF. Our findings of distinct improvements in haemodynamics and NT-pro-BNP are consistent with these studies and suggest that the benefits in chronic stable HF may be mediated similarly to that in ADHF and may be extended to include other stable patients irrespective of levosimendan use. However, in the largest trial to date, LevoRep,<sup>23</sup> 120 outpatients were randomized to 6 h of 0.2 µg/kg/min infusions of levosimendan or placebo at 2 week intervals over 6 weeks without effect on the 6 min walk test or Kansas City Cardiomyopathy Questionnaire. However, the 65-patient LION-HEART trial did show a reduction in NT-pro-BNP area under the curve and was also promising in secondary morbidity outcomes, but the rationale for, indications for, and effects of as needed or repetitive treatments with levosimendan require further study.

These conflicting data suggest that certain clinical phenotypes may benefit whereas others may not and that these cannot be distinguished by simple inclusion criteria such as EF, NYHA class, and symptoms (such as the 6 min walk test as in LevoRep). Similarly to other HF settings, we attempted to identify predictors of levosimendan response, so as to “enrich” and improve the design of future trials. However,

our small study could not identify any single clinical or haemodynamic factor that predicts levosimendan efficacy. Further studies are warranted to determine predictors of haemodynamic response in this patient population.

## Limitations

Our study is limited by the small sample size, and our findings need confirmation in a larger study. The small sample size did not allow meaningful assessment of outcomes such as quality of life or reaching transplantation. We used PBF as a surrogate for CO, which due to shunts may entail limitations for cross-sectional between-patient comparisons but is reliable for within-patient, changes over time, the primary measure in our study. Moreover, electrocardiography and echocardiographic examination were not performed in the current study; subsequently, they were not included in our discussion about the haemodynamic effect of a single-dose levosimendan. Another limitation is that we did not use a control group with placebo infusion. Therefore, the results from this study may have been subjected to a placebo effect. The placebo effect may have affected the degree of the positive effect of a single-dose levosimendan but cannot explain the whole effect. In uncontrolled settings, a placebo effect cannot be ruled out, but in prior randomized trials, placebo has not affected CO or stroke volume.<sup>28,32</sup>

## Conclusions

In patients with advanced but stable HF with reduced EF, levosimendan was associated with improved haemodynamics. However, we could not identify predictors of levosimendan’s haemodynamic effect.

## Conflict of interest

L. H. L.: No disclosures directly related to the present work. Unrelated disclosures are as follows: Research grants from Astra Zeneca and Boston Scientific; consulting or speaker’s honoraria from Novartis, Astra Zeneca, Bayer, St Jude, Medtronic, and Vifor Pharma.

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