

The Potential Beneficial Effect of Levosimendan in Milrinone-treated Advanced Heart Failure Patients

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Research Article

Keywords: Heart Failure, Inotropic support, levosimendan, milrinone, Hospitalization, QOL

Posted Date: March 2nd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-251993/v1>

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Abstract

Background

Routine, short-term use of inotropic agents is still applied in advanced heart failure (HF) patients either as a bridge to definitive treatment or as a mean to improve quality of life, despite the paucity of scientific evidence. Intermittent levosimendan was shown to be efficacious compared to placebo in advanced HF patients, however no prospective data comparing it to other inotropes and in particular, to milrinone are available. We aimed to assess the clinical effects of intermittent levosimendan in a small group of milrinone-treated advanced HF patients.

Methods

This was a prospective, un-blinded study. Consecutive ambulatory advanced HF patients intermittently treated with ≥ 4 cycles of once-weekly 6-hours 0.25–0.5 mg/kg/min milrinone at our HF outpatient clinic, were switched to levosimendan. All patients were evaluated using B-natriuretic peptide (BNP) levels, echocardiography, cardio-pulmonary exercise test and HF questionnaire before and after 4 weeks of intermittent once-weekly 6-hours therapy with levosimendan 0.1–0.2 mcg/kg/min.

Results

The cohort included 11 patients, 10 men, mean age 76 ± 12 years. After 4 weeks of levosimendan therapy, Vo_2 max improved by a mean of 2.28 ml/kg [95% CI -0.22-3.38, $p = 0.05$], BNP levels decreased from a median of 1015 ng/l [261–1035] to 719 ng/l [294–739], ($p < 0.01$) and the sum scores of EQ-5D-5L non-significantly improved by a median of 2 points [95% CI -4.17-0.37, $p = 0.09$]. On echocardiography, tricuspid annulus tissue Doppler increased by an average of 3 cm/s [95% CI 0.16–2.10, $p = 0.03$]. In addition, HF-related hospitalizations numerically decreased after switching to levosimendan.

Conclusion

In this small-scale, prospective study, we observed improvement in laboratory, echocardiographic and exercise capacity parameters in milrinone-treated advanced HF patients who were switched to levosimendan.

Introduction

Routine, short-term inotropic therapy (i.e. dobutamine, milrinone) is applied for advanced heart failure (HF) patients either as a bridge to definitive treatment or as a mean to improve quality of life (QOL) in many centers world-wide, despite the paucity of scientific evidence supporting its use. While no specific inotrope was conclusively found to have superior outcomes in advanced HF, both mechanistic and small clinical studies have suggested that milrinone and levosimendan have a better safety and efficacy profile in these patients¹⁻⁴. Interestingly, despite its short half-life, repeated milrinone therapy was found to have a protracted hemodynamic effect lasting days after its administration, making it a possibly useful agent for intermittent use⁵.

Levosimendan, through its unique effect on calcium sensitization (rather than increased calcium levels), was found to induce a limited increase in myocardial oxygen demand and to be less arrhythmogenic compared with other inotropic agents^{1,3,4,6,7}. Additionally, due to the protracted half-life of its metabolite (i.e. OR 1986, half-life 80 ± 36 hours), levosimendan shows persistent hemodynamic effects despite intermittent administration^{1,3,4,7,8} and was recently found to improve QOL and to reduce HF hospitalizations in advanced HF patients³.

However, with the exception of short-term hemodynamic studies⁶, no trial has compared HF measures in milrinone vs levosimendan treated patients.

Based on these findings, we have decided to switch our intermittently milrinone-treated advanced HF patients to levosimendan and prospectively compared laboratory, imaging and exercise capacity measures before and after exposure to levosimendan.

Methods

This was a prospective, unblinded crossover study performed at our HF outpatient clinic at the Tel-Aviv Medical Center, a tertiary hospital in Tel-Aviv, Israel. As part of our local HF registry, all research volunteers agreed to participate in this study, Informed consent was obtained, allowing anonymous prospective data collection including demographic, clinical, laboratory and imaging parameters. Study protocol was approved by an institutional Helsinki board in adherence to its guidelines. Our HF outpatient clinic is based on routine visits at time interval of 7-14 days during which the patients are seen and examined by a dedicated team of nurses and physicians experienced with HF treatment. Laboratory and imaging evaluation is done according to patient's status, including lung and abdominal ultrasound. Appropriate therapy (e.g. inotropes, diuretics, iron) is applied following clinical evaluation and tests results and may also comprise of pleural and/or peritoneal taps. The main inotropic agent used at our clinic is milrinone, given at intervals of 3-14 days.

Study population

Patients at our HF outpatient clinic receive intermittent inotropic (i.e. milrinone) support if they fulfill the following criteria for advanced HF: (a) left ventricular ejection fraction (LVEF) $< 35\%$ (b) elevated brain natriuretic peptide (BNP) levels (c) are either severely symptomatic (i.e. NYHA class III-IV) or experienced > 1

hospitalizations due to HF decompensation in the past 12 months despite maximally tolerated GDMT (d) have experienced symptomatic improvement following milrinone therapy.

In the current analysis, we included all patients who received at least 4 cycles of once-weekly milrinone treatment and were switched from milrinone therapy to levosimendan between August 2019 and April 2020. None of the patients were previously exposed to levosimendan.

17 patients at our outpatient clinic fulfilled these criteria. However, few were excluded due to the following reasons – 1 patient had advanced renal failure (i.e. glomerular filtration rate < 30 ml/min); 1 patient had systolic blood pressure < 90 mm/Hg; 2 patients experienced multiple non-cardiac hospitalizations making them inaccessible for the trial protocol, 1 patient was unable to arrive on the specified dates of levosimendan administration. One additional patient received only one dose of levosimendan and was scheduled to undergo LVAD implantation due to rapid deterioration. He subsequently suffered HF exacerbation, ventricular tachycardia with repeated ICD shocks and eventually died during hospitalization. This patient was not included in the data analysis as he received only one dose of levosimendan, leaving 11 patients who completed the planned protocol.

Follow up and Levosimendan protocol

The following surveillance is part of the comprehensive treatment given at our outpatient clinic -

1. During inotrope infusion, participants are closely monitored both with ECG monitors and vital signs.
2. In patients who have been treated with once-weekly 6-hours intermittent intravenous milrinone 0.25-0.5 mcg/kg/min for >4 consecutive clinic visits, clinical parameters were collected within 24-72 hours after last inotropic dose, including:
 - I. Echocardiography data.
 - II. Cardiopulmonary exercise test (CPET) data.
 - III. BNP levels.
 - IV. Heart failure QOL questionnaire (Hebrew version of EQ-5D-5L questionnaire)⁹.
3. During routine clinic visit, 7-10 days after the last dose of milrinone, patients received intravenous levosimendan 0.1-0.2 mcg/kg/min for a 6-hour period to be repeated every week for 4 weeks.
4. After this 4-week period of levosimendan treatment, all the tests described in section 2 were repeated (**Figure 1**).

Endpoints:

Endpoints included:

1. Changes in QOL (i.e. E1-5D-5L sum scores for all questions and general medical assessment) score.
2. Maximal oxygen consumption ($\dot{V}O_2$ max) and exercise duration on CPET.
3. BNP levels.
4. Echocardiographic parameters including - LVEF, the ratio of early mitral inflow velocity to mitral annulus tissue Doppler (E/e' ratio) and to mitral inflow during atrial contraction (E/A) and deceleration time of the E wave, tricuspid annulus plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (SPAP).

Statistical methods

Categorical data were compared using the Chi square test or Fischer exact test. Continuous data were compared with the student t test, and specifically the change of continuous and ordinal data pre and post Levosimendan treatment was compared using the paired sample T test. We used SPSS statistics software version 25.

Results

Eleven patients were included in the study, mean age was 76 ± 12 years and 10 (91%) were males. Ischemic cardiomyopathy was the baseline etiology in 9 (82%) patients, 10 (91%) had chronic kidney disease and the overall estimated creatinine clearance was 38 ± 14 ml/kg/min. One patient had an implanted pacemaker and all others had implantable cardioverter defibrillators without (4, 36%) or with (6, 54%) cardiac resynchronization therapy, (**Table 1**).

At baseline, all patients received beta blockers and angiotensin receptor neprilysin inhibitor therapy. Six (54%) were treated with mineralocorticoid receptor antagonists and all patients received furosemide at a mean dose of $90 (\pm 53)$ mg, (**Table 1**).

Individual pre-specified endpoints pre and post levosimendan are described in **Table 2** and **Figure 2**. In summary, 9/11 (82%) patients showed reductions in BNP levels on levosimendan treatment, 8/11 (82%) patients had an improvement in the sum of scores of the EQ-5D-5L QOL questionnaire, whereas the visual assessment scale improved in 4 and remained the same in 2 patients. $\dot{V}O_2$ max improved in 8/9 (89%) patients who completed both CPETs (pre and post levosimendan). When evaluating the impact of levosimendan treatment on the pre-specified endpoints in the entire group, $\dot{V}O_2$ max improved by a mean of 2.28 ml/kg [95% CI -0.22-3.38, $p=0.05$]. BNP levels decreased from a median of 1015 ng/l [261-1035] to 719 ng/l [294-739], ($p<0.01$) and the sum scores of EQ-5D-5L improved by a median of 2 points [95% CI -4.17-0.37, $p=0.09$]. On echocardiography LVEF, SPAP and TAPSE did not change significantly, whereas the

tissue Doppler of the tricuspid lateral annulus improved by an average of 3 cm/s [95% CI 0.16-2.10, p=0.03], (**Table 3**). Diastolic function showed signs of improvement in several parameters, the average E/e' ratio decreased from 14±5 to 10±8 (p=0.054) and the E/A ratio decreased from 1.2±0.7 to 0.8±0.4 (p=0.343) on Levosimendan treatment.

During a median follow-up of 140 days [IQR 23-203] on Levosimendan, one patient received an LVAD and one patient was hospitalized twice due to HF exacerbations, whereas during a shorter follow-up of 83 days [23-140] on Milrinone (pre-Levosimendan), 3 patients were hospitalized due to HF exacerbation and 2 of them were hospitalized twice (**Table 4**).

Discussion

In this small cohort of inotrope-treated advanced HF patients, we observed improvement in major aspects of HF including QOL, echocardiographic parameters, exercise capacity and BNP levels after conversion from milrinone to levosimendan intermittent treatment.

Cyclic adenosine monophosphate (cAMP) based agents represent the core of inotropic therapy in advanced HF. These drugs were shown to reduce left ventricular end diastolic and pulmonary capillary wedge pressures, to increase cardiac output, to lower BNP levels^{10,11} and to improve advanced HF patients symptoms and functional capacity¹². Nevertheless, the above described hemodynamic benefits did not translate into improved clinical outcomes^{13,14} and accordingly, the Food and Drug Administration states that "*cAMP-dependent inotropes were consistently associated with increased risks of hospitalization and death. Patients with NYHA class IV symptoms appeared to be at particular risk.*" Notably, despite these recommendations, inotropes are still being applied in many HF patients and according to the 2014 Get With The Guidelines Heart Failure registry, depending on region and hospital, 1.3-32.9% of HF patients were treated with inotropes during their hospitalization⁷. This contradiction probably generates from the notion that conclusions drawn from studies evaluating clinical outcomes in inotrope-treated HF patients do not necessarily apply to contemporary practice which incorporates proven therapies for sudden cardiac death prevention. It might also signal that there is an unmet therapeutic need for these patients, for which inotropes represent a reasonable option.

Nevertheless, inotropic therapy is not risk-free, and additionally, the short half-life of most inotropes (e.g. dobutamine: 2 minutes) requires a continuous intravenous drip to maintain hemodynamic effect (of note, previous version of oral milrinone fell out of favor following the results of clinical trials^{14,15}).

These limitations can be mitigated, at least in part, by levosimendan, a calcium sensitizer which also has peripheral potassium channel activating effect and mild phosphodiesterase inhibition¹⁶. Combined, these mechanisms translate into increased cardiac contractility and peripheral and pulmonary vasodilation. Because levosimendan enhances the cardiac contractility apparatus without increasing intracellular calcium levels¹⁷, it is probably less arrhythmogenic compared with other inotropes and does not significantly increase myocardial oxygen consumption, an appealing tribute for patients with failing and exhaustive myocardium^{18,19}. Studies evaluating the duration of levosimendan's hemodynamic effects demonstrated that it lasts longer than anticipated. PCWP decreased by an average of 25% and was maintained for an average of 8 days and cardiac output increased by 23% and remained elevated for 12 days. These effects are probably the results of the continued potency of levosimendan's active metabolites OR 1896 and OR 1855²⁰.

Initial clinical studies showed promising results. In the Levosimendan Infusion versus Dobutamine (LIDO) study⁴, 203 acutely decompensated HF patients (with low CO according to right heart catheterization) were randomly assigned to levosimendan vs dobutamine. Levosimendan-treated patients were alive and out of hospital for a significantly longer period of time. Thirty-day mortality was 17% and 8% in dobutamine vs levosimendan treated patients respectively (p=0.049) and when the follow-up was retrospectively examined for 6 months, rates of death were 38% and 26% respectively (p=0.029). The Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE) I and II studies²¹ and the Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE)²² study examined the effect of levosimendan vs placebo and dobutamine respectively. The REVIVE studies included 600 patients with acute decompensated HF. Numerically, but not statistically significant, higher rates of mortality were found in the levosimendan group (12% vs 15%, p=0.21), whereas in the SURVIVE study (n=1327), mortality rates were similar in dobutamine vs levosimendan treated patients (28% and 26% respectively, p=0.4). Of note, compared with either placebo or dobutamine, levosimendan-treated patients had lower BNP levels and better symptomatic improvement.

Importantly, opposed to previous inotrope studies, which used continuous intravenous drip, all of the above described levosimendan trials used a single dose of the studied drug given over 6-24 hours, and consequently, none could evaluate the long-term effect of an intermittent short-term levosimendan drip on clinical outcomes. In the Pulsed Infusions of Levosimendan in Outpatients with Advanced Heart Failure (LevoRep) study, 120 patients were randomly assigned to 4 cycles 6-hours pulse administration of 0.2mcg/kg/hour levosimendan infusion vs placebo in 2 weeks intervals and then followed for another 18 weeks². By the end of the 24-week study period, no statistically significant improvement was shown in either 6-minute walk distance or HF questionnaire between levosimendan and placebo treated patients. The study was criticized due to the prolonged lag between drug administration and endpoint evaluation. The Levosimendan Intermittent administration in Outpatients: effects on Natriuretic peptides in advanced chronic HEART failure (LION-HEART) study randomized 69 patients in 2:1 fashion to 6 cycles 6-hours pulse administration of 0.2mcg/kg/hour levosimendan infusion vs placebo in 2 weeks interval³. The primary endpoint of the study (change in NT-proBNP levels) was evaluated at the end of the 12-week treatment period and showed a significant difference between levosimendan and placebo treated patients (344×10^3 ; 95% CI $[283 \times 10^3 - 404 \times 10^3]$ vs. 535×10^3 $[443 \times 10^3 - 626 \times 10^3]$, p=0.003). Furthermore, hospital admissions were reduced in the levosimendan arm (hazard ratio 0.25; 95% CI 0.11–0.56; P =0.001).

These data, make levosimendan an attractive agent for our ambulatory care clinic patients, who are mainly given intermittent inotropic support, and based on these observations we have decided to introduce levosimendan as a standard treatment for our inotrope treated patients. To the best of our knowledge, excluding short-term hemodynamic studies conducted in cardiac surgery patients⁶, no study was done to compare clinical outcomes in milrinone vs levosimendan treated HF patients. Though our cohort included only a small group of patients with a medium-term follow up, we were able to extract

comprehensive data regarding neurohormonal parameters, echocardiographic indices, oxygen consumption, functional status and hospital admissions. None of the patients who completed 4 cycles of Levosimendan in our group died or required renal replacement therapy. Compared with intermittent milrinone therapy, levosimendan therapy was associated with neutral effect on left ventricular systolic echocardiographic parameters and exercise duration whereas an improvement in neurohormonal status, QOL, oxygen consumption, right ventricular systolic function and a trend toward better diastolic function was shown. With regards to clinical endpoints, numerically more HF hospitalizations were seen during milrinone vs. levosimendan treatment, despite a shorter duration of follow-up on milrinone.

As in other scenarios of advanced HF treatment, our study represents a specific approach which might not be appropriate for every center. Our facility incorporates an outpatient clinic which allows patients to be treated by health care providers who are experienced with the care of advanced HF. Intravenous drugs (e.g. iron, diuretics) are routinely applied, pleural and peritoneal taps are being done when needed and inotropes are given in a proper settings. As previously shown²³, and regardless of inotropic therapy, the ability to closely monitor and treat advanced HF patients probably has an important role in patient management and improves outcomes.

Our study has several limitations; first, the possibility of selection bias due to lack of randomization and the crossover nature of the study. However, this crossover represents a carefully scheduled switch from one inotrope to another in the most advanced HF patients treated as outpatients at our center, the majority of them were on optimal guideline-directed medical therapy including beta blockers, RAAS inhibitors with neprilysin inhibitors and device therapy as indicated. A second limitation is the fact that neither the patients nor the treating team were blinded to the change of treatments. Third, our cohort was small and the duration of follow up was limited – echocardiography, laboratory and CPET were repeated after 4 cycles of treatment and clinical follow-up was at a median of 140 days. These limitations might be properly addressed in a large, randomized study. Last, we cannot exclude the possibility that the patient who died (and was not included in data analysis) suffered an adverse event induced by levosimendan.

In conclusion, this small prospective cross-over study showed superiority of levosimendan compared to milrinone in significant aspects of advanced HF therapy which may deserve further investigation.

Declarations

Funding – No funding received

Conflicts of interest/Competing interests: The authors report no financial relationships or conflicts of interest regarding the content herein

Ethics approval (include appropriate approvals or waivers)

Consent to participate: all research volunteers agreed to participate, informed consent was obtained, and study protocol was approved by an institutional Helsinki board in adherence to its guidelines

Consent for publication: the authors agree to publish this paper

Data availability: all data used for drafting this manuscript including statistical analysis, interpretation as well as the lab results and functional tests is available upon request by e-mail

Authors contribution:

AM – study design, manuscript drafting, statistical analysis

SF – study design, manuscript drafting, editing

ML- date gathering, manuscript editing and review

BS- date gathering, manuscript editing and review

OS- date gathering, manuscript editing and review

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References

1. Hashim, T. *et al.* Clinical Characteristics and Outcomes of Intravenous Inotropic Therapy in Advanced Heart Failure. *Circ Heart Fail.* **8**, 880–886 (2015).
2. Altenberger, J. *et al.* Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial. *European journal of heart failure.* **16**, 898–906 (2014).
3. Comín-Colet, J. *et al.* Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. *European journal of heart failure.* **20**, 1128–1136 (2018).
4. Follath, F. *et al.* Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet (London, England).* **360**, 196–202 (2002).
5. Hatzizacharias, A. *et al.* Intermittent milrinone effect on long-term hemodynamic profile in patients with severe congestive heart failure. *American heart journal.* **138**, 241–246 (1999).
6. Mishra, A., Kumar, B., Dutta, V., Arya, V. K. & Mishra, A. K. Comparative Effect of Levosimendan and Milrinone in Cardiac Surgery Patients With Pulmonary Hypertension and Left Ventricular Dysfunction. *J Cardiothorac Vasc Anesth.* **30**, 639–646 (2016).
7. Allen, L. A. *et al.* Hospital variation in intravenous inotrope use for patients hospitalized with heart failure: insights from Get With The Guidelines. *Circ Heart Fail.* **7**, 251–260 (2014).
8. Lilleberg, J. *et al.* Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure. *European journal of heart failure.* **9**, 75–82 (2007).
9. Herdman, M. *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* **20**, 1727–1736 (2011).
10. Maskin, C. S., Sinoway, L., Chadwick, B., Sonnenblick, E. H. & Le Jemtel, T. H. Sustained hemodynamic and clinical effects of a new cardiotoxic agent, WIN 47203, in patients with severe congestive heart failure. *Circulation.* **67**, 1065–1070 (1983).
11. Benotti, J. R., Grossman, W., Braunwald, E., Davolos, D. D. & Alousi, A. A. Hemodynamic assessment of amrinone. A new inotropic agent. *The New England journal of medicine.* **299**, 1373–1377 (1978).
12. Simonton, C. A. *et al.* Milrinone in congestive heart failure: acute and chronic hemodynamic and clinical evaluation. *Journal of the American College of Cardiology.* **6**, 453–459 (1985).
13. Anderson, J. L., Askins, J. C., Gilbert, E. M., Menlove, R. L. & Lutz, J. R. Occurrence of ventricular arrhythmias in patients receiving acute and chronic infusions of milrinone. *American heart journal.* **111**, 466–474 (1986).
14. Packer, M. *et al.* and *et al.* Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *The New England journal of medicine.* **325**, 1468–1475 (1991).
15. Massie, B. *et al.* Long-term oral administration of amrinone for congestive heart failure: lack of efficacy in a multicenter controlled trial. *Circulation.* **71**, 963–971 (1985).
16. Nieminen, M. S. *et al.* Levosimendan: current data, clinical use and future development. *Heart Lung Vessel.* **5**, 227–245 (2013).
17. Sorsa, T., Pollesello, P. & Solaro, R. J. The contractile apparatus as a target for drugs against heart failure: interaction of levosimendan, a calcium sensitiser, with cardiac troponin c. *Mol Cell Biochem.* **266**, 87–107 (2004).
18. Mavrogeni, S. *et al.* A 6-month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure. *J Card Fail.* **13**, 556–559 (2007).
19. Ukkonen, H. *et al.* Myocardial efficiency during levosimendan infusion in congestive heart failure. *Clin Pharmacol Ther.* **68**, 522–531 (2000).
20. Erdei, N., Papp, Z., Pollesello, P., Edes, I. & Bagi, Z. The levosimendan metabolite OR-1896 elicits vasodilation by activating the K(ATP) and BK(Ca) channels in rat isolated arterioles. *Br J Pharmacol.* **148**, 696–702 (2006).
21. Packer, M. *et al.* Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail.* **1**, 103–111 (2013).
22. Mebazaa, A. *et al.* Pöder P and Kivikko M. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *Jama.* **297**, 1883–1891 (2007).
23. Van Spall, H. G. C. *et al.* Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *European journal of heart failure.* **19**, 1427–1443 (2017).

Tables

Table 1
Baseline characteristics

		Baseline value
Age		76±12
Gender, male		10 (91%)
BMI, kg/m ²		27.3±4.3
Ischemic heart disease		9 (82%)
Blood pressure, mm/Hg		111/61 ± 20/12
Past stroke		3 (27%)
Diabetes Mellitus		4 (36%)
Hypertension		10 (91%)
Chronic kidney disease		10 (91%)
Past smoking		5 (45%)
Creatinine mg/dl (eGFR ml/kg/min)		1.9±0.6 (38±14)
Hemoglobin, mg/dl		13±2
Hemoglobin A1c, %		6.5±1.4
B-type natriuretic peptide, ng/L		723 [261,1035]
Device	Pacemaker	1 (9%)
	ICD	4 (36%)
	CRT-D	6 (55%)
Medications	ACE-i/ARB	0
	ARNI, (dosage in mg)	100% (241±97)
	MRA (dosage in mg)	55% (20±8)
	BB (dosage in mg)	100% (4.2±1.2)
	Furosemide (dosage in mg)	100% (90±53)
	Digoxin	5 (45%)
	SGLT2-i	2 (18%)
	Anti platelets	9 (82%)
	Statins	9 (82%)
	Insulin	4 (36%)

ACE-I- angiotensin converting enzyme inhibitor, ARB - angiotensin receptor blocker, ARNI- sacubitril/valsartan, BB-beta blockers (in bisoprolol equivalent dosage), BMI- body mass index, CRT-D- cardiac resynchronization therapy with defibrillator, ICD - intra cardiac defibrillator, MRA -mineralocorticoid receptor antagonist.

Table 2
Patients Main Outcome Measures Pre and Post 4 weeks of Levosimendan Treatment

Patient#	Pre Levosimendan									Post Levosimendan						
	QOL	Sum of scores	Vo2 max (ml/kg)	Exercise duration (min)	EF (%)	Diastolic grade	PAP	Cr.	BNP	QOL	Sum of scores	Vo2 max (ml/kg)	Exercise duration (min)	EF (%)	Diastolic grade	PAI
1	5	17	13.8	4.35	30	1	27	1.8	1035	50	9	13.9	4.01	25	1	26
2	70	12	13.1	6.11	25	2	27	1.6	221	80	11	15.6	6.26	30	1	N/A
3	60	14	11.3	2.31	35	2	70	1.9	4774	27	11	15	5.51	35	NI	65
4	60	13	10.6	3.08	20	0	46	1.4	1025	98	7	14.7	4.27	20	NI	27
5	80	7	18.1	7.34	30	2	42	1.6	377	100	6	20.7	7.19	25	NI	35
6	90	5	13.9	5.35	35	1	49	2.6	851	80	8	14.2	6.29	40	NI	55
7	75	11	-	-	35	1	30	3.2	122	70	9	-	-	25	2	41
8	50	12	14.6	4.02	45	2	39	1.1	511	50	11	12.4	3.06	45	-	34
9	40	17	10	5.00	35	2	43	2.1	723	55	16	10	3.29	35	2	43
10	65	11	-	-	30	Afib	70	2.2	1275	60	12	-	-	25	Afib	73
11	-	-	10	5.27	30	1	20	1.6	265	65	11	14	6.58	30	1	27

BNP- B type Natriuretic Peptide, Cr.- Creatinine (mg/dl), EF- Ejection fraction, PAP- pulmonary artery systolic pressure (mm/Hg), QOL- quality of life (0-100).

Table 3
Outcomes Comparison of Patients Baseline vs. Post 4 weeks of Levosimendan Treatment

		Pre Levosimendan	Post Levosimendan	t [95% CI]	P value
CPET	Exercise duration, min	4.53±1.32	5.21±1.35	0.93 [-0.40-1.35]	0.38
	Vo ₂ max, ml/kg/min	12.82±2.65	14.50±2.86	2.28 [-0.22-3.38]	0.05
QOL	Scale (0-100)	60±24	67±23	1 [-9.14-24.14]	0.34
	Sum of scores (5-25)	12±4	10±3	2 [-4.17-0.37]	0.09
Lab	BNP, ng/l	1015 [261-1035]	719 [294-739]		< 0.01
Echo	Ejection Fraction, %	32±6	31±8	-1 [-4.40-1.68]	0.34
	PAP, mm/Hg	44±17	43±17	0 [-6.89-5.10]	0.74
	TAPSE, mm	18±5	18±5	0 [-2.36-3.16]	0.75
	S', cm/s	9±3	10±3	3 [0.16-2.10]	0.03

BNP- B type Natriuretic Peptide, CPET- cardio pulmonary exercise test, Echo - echocardiography, Lab- laboratory, PAP- pulmonary artery systolic pressure (mm/Hg), QOL- quality of life (0-100), TAPSE - tricuspid annular plane systolic excursion.

Table 4
Clinical Outcomes Pre and Post Levosimendan Treatment.

Patient#	Pre Levosimendan				Post Levosimendan			
	Days on Milrinone	HFH	LVAD	Death	Days on Levosimendan	HFH	LVAD	Death
1	186	0	0	0	186	0	0	0
2	162	2	0	0	280	0	1	0
3	116	0	0	0	280	0	0	0
4	116	0	0	0	189	0	0	0
5	21	0	0	0	21	0	0	0
8	54	2	0	0	203	0	0	0
9	83	1	0	0	88	2	0	0
10	140	0	0	0	140	0	0	0
11	23	0	0	0	23	0	0	0
12	23	0	0	0	23	0	0	0
13	23	0	0	0	23	0	0	0

LVAD- Left Ventricular Assist Device, HFH - Heart Failure Hospitalizations

Figures

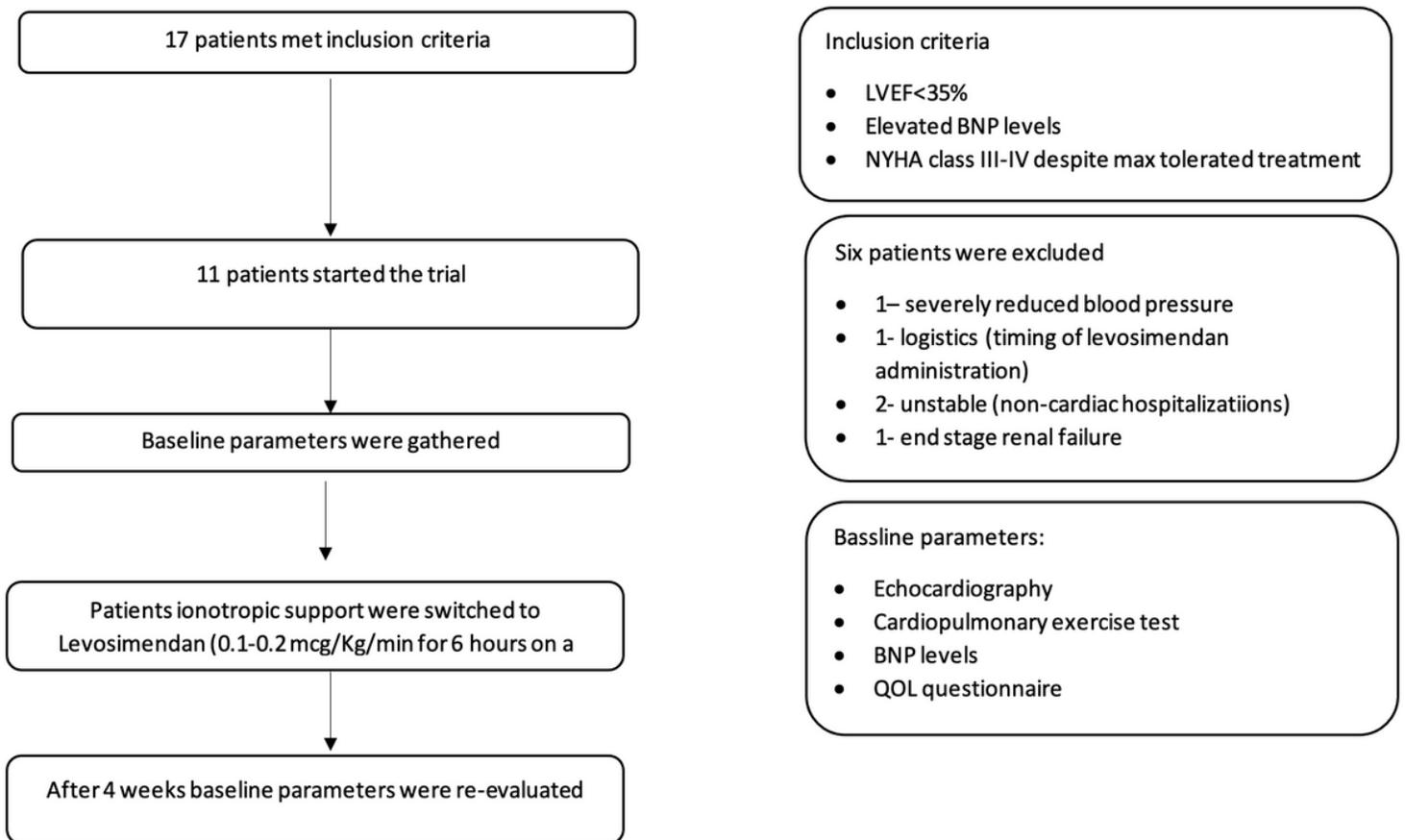


Figure 1
Study design. LVEF- left ventricular ejection fraction, BNP- B type Natriuretic Peptide, NYHA – New York Heart Association, CPET- cardio pulmonary exercise test, Echo – echocardiography, QOL- quality of life (0-100).

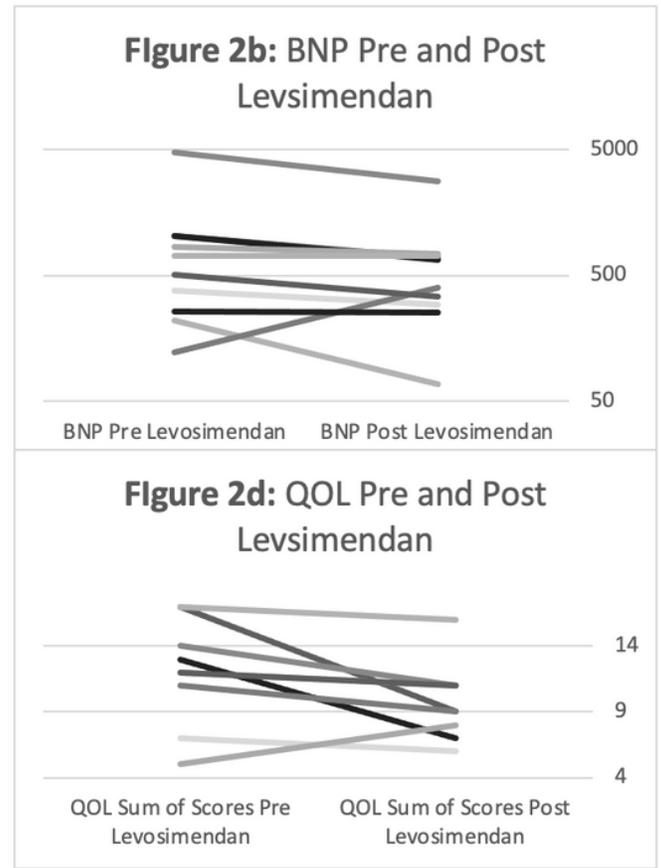
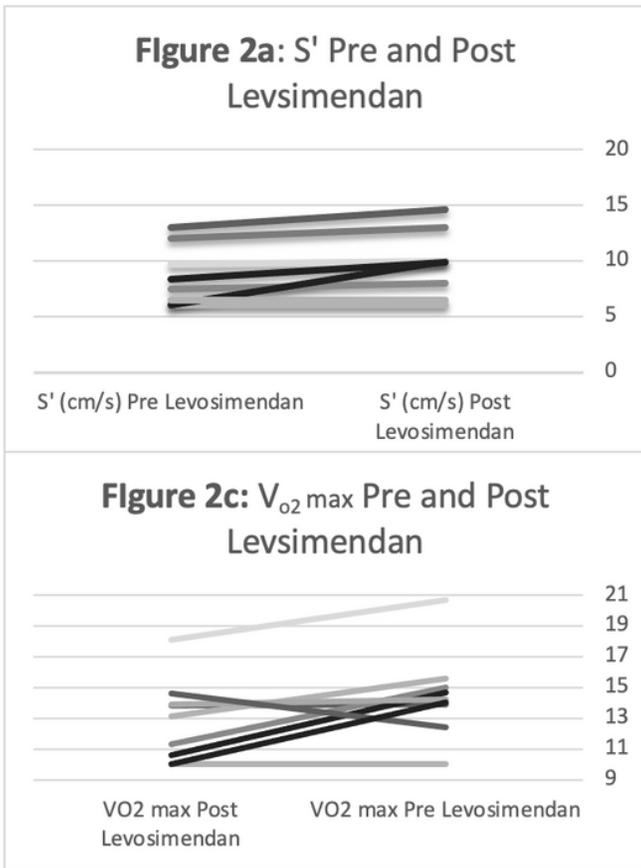


Figure 2

Main End Points Pre and Post Levosimendan Treatment. Figure 2a: Right ventricular systolic function as measure by S' wave pre Levosimendan (on Milrinone) and post 4 cycles of Levosimendan treatment. Figure 2b: B-type Natriuetic Peptide levels pre Levosimendan (on Milrinone) and post 4 cycles of Levosimendan treatment. Figure 2c: Vo2 max values pre Levosimendan (on Milrinone) and post 4 cycles of Levosimendan treatment. Figure 2d: Quality of Life (QOL) based on sum of scores of 5 questions in the EQ-5D-5L questionnaire.