Original Research

Prophylactic Preoperative Levosimendan Administration in Heart Failure Patients Undergoing Elective Non-Cardiac Surgery: A Preliminary Report

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Introduction: Preoperative optimization of cardiac failure (CF) patients undergoing non-cardiac surgery is of utmost importance. Levosimendan is a promising adjunct in our therapeutic repertoire for the treatment of CF; however, it has not been evaluated in CF patients undergoing non-cardiac surgery. Our objective was to evaluate the safety and efficacy of prophylactic preoperative levosimendan administration in these patients.

Methods: CF patients with ejection fraction <35% undergoing elective non-cardiac (abdominal) surgery during a 6-month-period were included in this prospective study. All patients, admitted to the Surgical Intensive Care Unit (SICU) one day preoperatively for levosimendan administration, received a bolus infusion (2.4 μg/kg) for 10 min followed by a 24-hour continuous infusion (0.1 μg/kg/min) at the end of which they were operated. Patients were under continuous hemodynamic monitoring in the SICU during levosimendan infusion and for 24 h post-infusion. Hemodynamic parameters, including heart rate, arterial pressure and pulmonary artery catheter data, were recorded before treatment, 10 min after drug initiation, and at 3-hour intervals to 24 h post-infusion. Echocardiography was performed before infusion and on the 7th post-infusion day.

Results: Nine patients were enrolled. Cardiac index (0-48 h, 95% CI: -2.790-0.432, $p<0.001$) and stroke volume index (0-48 h, 95% CI: -32.53-0.91, $p=0.01$) increased significantly at 24 h after drug initiation and remained increased for 24 h post-infusion. Systemic vascular resistance index decreased at 10 min and remained reduced during the whole observation period (0-48 h, 95% CI: 875.64-2378.14, $p<0.001$). Ejection fraction was significantly increased on the 7th post-infusion day (32.65 ± 7.32 vs. 20.89 ± 6.24, $p<0.05$). No adverse reactions, complications or deaths occurred during 30 days' follow up.

Conclusion: Prophylactic preoperative levosimendan treatment may be safe and efficient for the perioperative optimization of heart failure patients undergoing non-cardiac surgery.

Cardiac complications are a major cause of perioperative morbidity and mortality in patients undergoing non-cardiac surgery.[1-3] Furthermore, cardiac failure (CF) is a frequent and significant risk factor for postoperative cardiac complications and mortality.[2] It results in a twofold higher postoperative mortality after major non-cardiac surgery, compared to patients with coronary artery disease or the general population.[4] CF is an important public health problem, with a 6-10% incidence in the population over 65, and is one of the most common reasons for hospitalization among elderly adults.[2,3,5] Moreover, CF patients undergo non-cardiac surgery with an increased frequency due to their advanced age.[2,3] Preoperative optimization

of these patients is, therefore, of utmost importance; guidelines for the perioperative management of such patients, however, have not been clarified.

The prophylactic use of positive inotropic drugs for the management of CF patients remains controversial, since their efficacy is debatable and they have been associated with increased myocardial oxygen consumption, arrhythmia risk, and mortality.[3,6] In contrast, levosimendan, a novel myofilament calcium sensitizer, is a new positive inotrope that has been shown to safely improve cardiac performance and hemodynamics in CF patients without increasing the myocardial oxygen demand or causing arrhythmias.[7-10] The use of levosimendan for perioperative optimization of patients undergoing cardiac surgery has been reported in a few studies with promising results;[11-15] however, it has not been thoroughly evaluated in CF patients undergoing non-cardiac surgery. The objective of this prospective study was to evaluate the safety and efficacy of prophylactic preoperative levosimendan administration in these patients. We report our results regarding the patients' hemodynamics, cardiac performance, adverse effects, perioperative morbidity, and outcome during 30 days' follow up.

Methods

Study design and patient population

This was a prospective study conducted in the Surgical Intensive Care Unit (SICU), 1st Department of Propaedeutic Surgery of the University of Athens, in the Hippokrateion Hospital, Athens, Greece, from 1st July to 31st December, 2004. Institutional Review Board approval was obtained prior to study initiation and written, informed consent was signed in all cases. Patients suffering from chronic CF, with left ventricular ejection fraction <35%, who were scheduled for elective non-cardiac surgery, were included in our study. Exclusion criteria were: restrictive or obstructive cardiomyopathy, severe cardiac valvular disease, history of atrial fibrillation, ventricular tachycardia or fibrillation, resting systolic arterial pressure <80 mmHg, second or third degree atrioventricular block, severe hepatic cirrhosis (defined as class C according to the Child-Pugh scoring system[16]), and severe renal failure (defined as creatinine clearance less than 30 ml/min).

Protocol

Preoperative risk stratification was performed according to the Goldman Cardiac Risk Index,[17] New York Heart Association (NYHA),[18] and American Society of Anesthesiologists (ASA) classification.[19] All study patients were admitted to our SICU one day before the operation for levosimendan administration and close hemodynamic monitoring, including continuous heart rate monitoring via electrocardiogram, arterial blood pressure via a radial artery catheter, urine output through a bladder catheter, pulse oximetry, and pulmonary artery catheter data. Blood gas analysis was performed every 3 hours and blood tests every 12 hours, including analysis of white blood cells, hematocrit, hemoglobin, platelets, coagulation, glucose, electrolytes, amylase, lactic dehydrogenase, creatinine phosphokinase and creatinine phosphokinase-MB, troponin, urea, creatinine, and liver function tests. In addition, echocardiography was performed before levosimendan infusion.

After initiation of monitoring, levosimendan was administered. The levosimendan treatment protocol consisted of a bolus infusion (2.4 μg/kg) over 10 minutes followed by a 24-hour continuous infusion (0.1 μg/kg/min). Failure to achieve an increase in cardiac index >30% at 2 hours of infusion was grounds for doubling the continuous infusion dose; however, this dose increase was not needed for any patient. Criteria for dose reduction were hypotension (systolic arterial pressure <80 mmHg) and heart rate >120 beats/min lasting longer than 10 min, and arrhythmias. In case such findings continued after dose reduction or if anaphylactic or other adverse reactions occurred, the treatment protocol would immediately be terminated.

All patients were under continuous hemodynamic monitoring in the SICU prior to and during levosimendan administration. They were operated immediately after the end of infusion under the same hemodynamic monitoring, which was continued postoperatively in the SICU until 24 hours post-infusion. Patients were then discharged from the SICU to the ward. Non-invasive monitoring in the ward included heart rate, electrocardiogram, arterial pressure, pulse oximetry, and urine output every 3 hours, clinical evaluation by the same attending surgical team every 3 hours, blood gas analysis every 12 hours, and blood tests once daily. Patients were discharged from the hospital when ability to walk, oral uptake, voidance, and bowel function were normal, provided no complication had occurred. Repeat echocardiography was performed on the 7th post-infusion day. They were seen in our outpatients' clinic on the 7th, 14th, and 30th postoperative days.

Recorded data

Hemodynamic parameters were recorded before treatment, 10 min after drug initiation, and then at consecutive 3-hour intervals during the treatment protocol and until 24 hours post-infusion. Recorded variables were: heart rate (HR), systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure, cardiac index (CIx), stroke volume index (SVI), central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), systemic vascular resistance index (SVRI), and pulmonary vascular resistance index (PVRI). Ejection fraction (EF) was also recorded during echocardiography performed before levosimendan infusion and on repeat examination on the 7th post-infusion day.

Statistical analysis

Data are presented as mean ± SEM (standard error of the mean). Comparisons between recorded data before treatment, at 10 min of infusion, and every 3 hours until 24 hours post-infusion were performed; in addition, 7th post-infusion day EF values were compared to pre-infusion ones. Statistical analysis was conducted using Wilcoxon's signed rank test and the Bonferroni pairwise multiple comparison test. The level of statistical significance was $p<0.05$; 95% confidence intervals (95% CI) were also calculated.

Results

During the 6-month period, 9 patients were enrolled in the study. Patients' demographics, surgical procedures, and preoperative Goldman Cardiac Risk Index, NYHA functional class, and ASA physical status are shown in Table 1. The patients' mean age was 74.3 ± 6.4 years; 7 (77.8%) of them were men. Mean hospital stay was 4.5 ± 2.3 days.

Levosimendan administration was safe in all patients. Dose reduction or treatment withdrawal was not required in any patient. No patient developed arrhythmia or hypotension and no tachycardia over 120 beats/min was observed. In addition, no adverse drug reactions, complications or mortality occurred during 30 days' follow up.

Levosimendan resulted in a significant increase of EF on the 7th post-infusion day compared to the pre-infusion values (32.65 ± 7.32 vs. 20.89 ± 6.24, $p<0.05$). Moreover, a significant increase of CIx was observed at 24 h after infusion initiation and was sustained during the next 24 h after the end of infusion (0-48 h, 95% CI: -2.790-0.432, $p<0.001$, Table 2 & Figure 1). Additionally, SVI was significantly increased at 24 h after infusion initiation and remained significantly increased during the 24 post-infusion hours (0-48 h, 95% CI: -32.53-0.91, $p=0.01$, Table 3 & Figure 2). SVRI was significantly reduced at 10 min after initiation of infusion and remained significantly reduced during the whole observation period (0-48 h, 95% CI: 875.64-2378.14, $p<0.001$, Table 4 & Figure 3). Interestingly, a comparison between CIx, SVI, and SVRI values at the end of levosimendan infusion (immediately prior to operation) and the postoperative values did not show any statistical significance.

Levosimendan showed no significant effect on HR, SAP, DAP, or MAP (data not shown). In addition, no significant changes were identified regarding CVP, PAP, PCWP, and PVRI (data not shown).

Table 1. Demographics, surgical procedures, and preoperative risk stratification of the study patients.

Patients	Sex	Age	Operation	GCRI	NYHA	ASA
1	male	64	abdominal hernia repair	2	2	4
2	female	70	abdominal hernia repair	2	3	4
3	male	72	abdominal hernia repair	1	2	3
4	male	83	abdominal hernia repair	1	2	3
5	male	67	abdominal hernia repair	1	2	3
6	male	77	adhesiolysis	2	2	4
7	male	83	colon surgery (Hartmann's procedure)	3	2	4
8	female	75	biliary surgery(choledochojejunostomy)	3	2	4
9	male	78	open cholecystectomy	2	2	4

ASA – American Society of Anesthesiologists physical status; GCRI – Goldman Cardiac Risk Index; NYHA – New York Heart Association functional class.

Discussion

Cardiac complications are one of the most important sources of perioperative morbidity and mortality in patients undergoing non-cardiac surgery, making strategies to reduce perioperative cardiac events of utmost importance.[1-3,20,21] Preoperative cardiac risk assessment is essential for the identification of the patients at risk and of those clinical risk factors amenable to therapeutic perioperative interventions.[20] Perioperative cardiac evaluation and therapeutic strategies for optimization of cardiac performance and reduction of cardiac complications, however, are mostly focused on the management of myocardial ischemia and infarction, whereas insufficient data are available regarding the perioperative cardiac optimization of CF patients.

Heart failure, though, is a very important risk factor for mortality and cardiovascular complications after non-cardiac surgery.[2,4,21] Patients with preexisting CF undergoing non-cardiac surgery suffer substantial morbidity and mortality despite advances in perioperative care. The importance of CF as an independent risk factor is underlined by the fact that patients with coronary artery disease but without heart failure have a 30-day mortality rate similar to that of the general population.[2] A decreased preoperative ejection fraction has been associated with increased postoperative morbidity and mortality, while perioperative left ventricular dysfunction is one of the major predictors of postoperative cardiac complications.[22] However, there is still very little known about the effectiveness of preoperative medical therapy for the prevention of cardiac complications in such high-risk patients un-

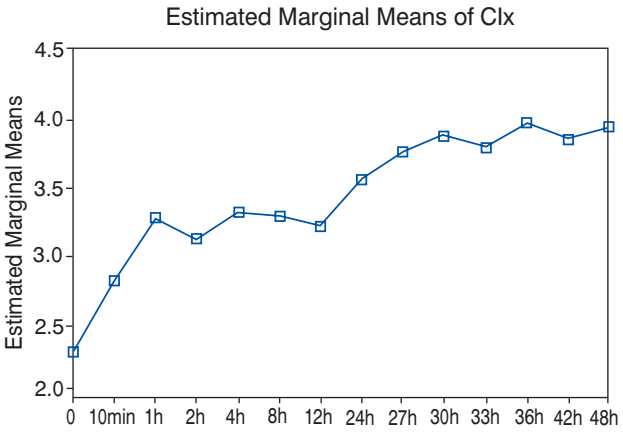

Figure 1. Changes in cardiac index (CIx) during and after levosimendan infusion.

Table 2. Changes in cardiac index (CIx) during and after levosimendan infusion.

Time after infusion initiation	CIx (L/min/m^2)	p	95% CI
0 min (pre-infusion value)	2.25 ± 0.42		
10 min	2.70 ± 0.28	0.467	-2.718-4.651
3 h	3.18 ± 0.43	0.154	-2.657-4.136
6 h	3.27 ± 0.37	0.105	-2.603-3.245
9 h	3.26 ± 0.59	0.112	-2.572-3.079
12 h	3.24 ± 0.60	0.115	-2.645-3.789
15 h	3.38 ± 0.41	0.084	-2.478-2.967
18 h	3.41 ± 0.57	0.069	-2.423-1.702
21 h	3.46 ± 0.39	0.061	-2.527-1.278
24 h	3.52 ± 0.64	0.028*	-2.412-0.443*
27 h	3.59 ± 0.73	0.003*	-2.612-0.254*
30 h	3.64 ± 0.81	0.001*	-2.723-0.366*
33 h	3.61 ± 0.62	0.002*	-2.634-0.277*
36 h	3.68 ± 0.54	0.000*	-2.812-0.454*
39 h	3.66 ± 0.75	0.001*	-2.657-0.382*
42 h	3.63 ± 0.66	0.001*	-2.701-0.343*
45 h	3.64 ± 0.73	0.001*	-2.737-0.415*
48 h	3.67 ± 0.78	0.000*	-2.790-0.432*

p and 95% CI values refer to comparison between each row's CIx and the pre-infusion value. * statistically significant.

Table 3. Changes in stroke volume index (SVI) during and after levosimendan infusion.

Time after infusion initiation	SVI (ml/m^2)	p	95% CI
0 min (pre-infusion value)	31.6 ± 4.7		
10 min	36.8 ± 5.4	0.483	-26.57-5.48
3 h	40.9 ± 5.8	0.147	-30.79-2.34
6 h	41.7 ± 6.2	0.095	-31.76-1.85
9 h	41.2 ± 5.9	0.164	-27.67-2.78
12 h	41.4 ± 7.3	0.153	-28.12-2.47
15 h	42.8 ± 7.8	0.108	-28.59-2.26
18 h	43.9 ± 6.9	0.086	-30.25-1.46
21 h	44.6 ± 8.4	0.071	-30.47-1.23
24 h	45.7 ± 8.1	0.003*	-33.56-0.38*
27 h	50.8 ± 8.6	0.002*	-34.91-0.45*
30 h	51.4 ± 7.7	0.001*	-35.31-0.69*
33 h	48.6 ± 6.5	0.031*	-34.20-0.58*
36 h	49.2 ± 8.4	0.010*	-34.53-0.91*
39 h	47.4 ± 9.2	0.010*	-33.49-0.88*
42 h	46.5 ± 7.9	0.010*	-33.73-0.82*
45 h	45.2 ± 7.6	0.010*	-33.07-0.76*
48 h	44.8 ± 8.3	0.010*	-32.53-0.91*

p and 95% CI values refer to comparison between each row's SVI and the pre-infusion value. * statistically significant.

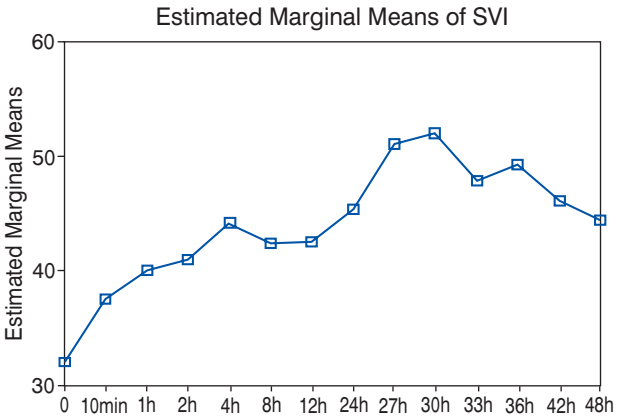

Figure 2. Changes in stroke volume index (SVI) during and after levosimendan infusion.

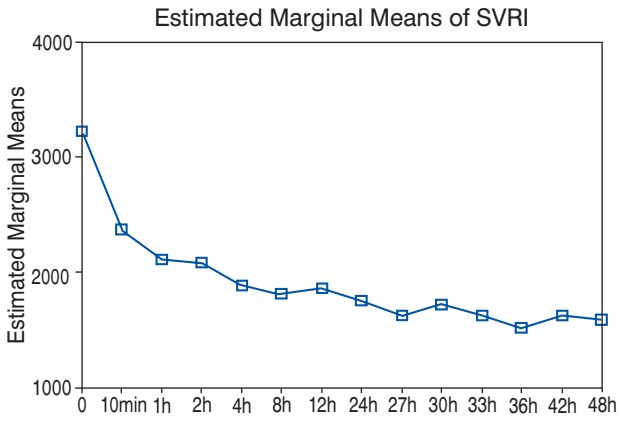

Figure 3. Changes in systemic vascular resistance index (SVRI) during and after infusion.

dergoing surgery. The lack of strict guidelines for preoperative optimization and perioperative management of CF patients underlines the complexity of the problem.

The prophylactic use of positive inotropic drugs for the management of CF patients remains controversial.[3,6,23] In a prospective randomized trial by Hayes et al, dobutamine not only failed to improve outcomes but was associated with increased mortality.[6] In contrast, in a retrospective study by Flancbaum et al it was suggested that preoperative correction of abnormal hemodynamic parameters with inotropes, crystalloids, packed red blood cells, and/or afterload reduction may reduce postoperative cardiovascular complications in patients who undergo major elective non-cardiac, non-thoracic surgical procedures.[23]

Calcium sensitizers are a new class of inotropic agents that enhance myocardial contractility through augmenting the sensitivity of the myofilaments to calcium, mainly by binding to troponin C. Levosimendan has unique characteristics among the group of sensitizers, as it stabilizes the interaction between calcium and troponin C by binding to troponin C in a calcium-dependent manner. Thus, it exerts its action throughout systole, when the concentration of calcium is high, without any adverse effects during diastole, when calcium concentration decreases.[10,24] It seems that the increased sensitivity to calcium is the main mechanism of action of levosimendan, while phosphodiesterase enzyme inhibition in the heart muscle is a less important mechanism.[10,25] In contrast to other agents, levosimendan has the advantage that the increased contractility is achieved without energy expenditure; it has been shown to improve cardiac performance and hemodynamics in CF patients without increasing myocardial oxygen consumption or showing any proarrhythmic effects.[7-10,25] At the same time, its inotropic support may not be affected in the failing heart because its inotropic action is independent of cyclic adenosine monophosphate generating pathways, which are downregulated in chronic heart failure.[24,25] Furthermore, it exerts vasodilatory effects through activation of adenosine triphosphate-dependent potassium channels in the vascular smooth

Table 4. Changes in systemic vascular resistance index (SVRI) during and after infusion.

Time after infusion initiation	SVRI ($dyn.s.cm^{-5}.m^{-2}$)	P	95% CI
0min (pre-infusion value)	3125.6 ± 453.2		
10 min	2341.7 ± 367.6	0.009*	98.75-1601.25*
3 h	2052.4 ± 318.3	0.000*	352.20-1854.69*
6 h	1984.5 ± 303.2	0.000*	579.98-2082.47*
9 h	1875.2 ± 280.8	0.000*	644.20-2146.69*
12 h	1905.7 ± 294.6	0.000*	605.42-2107.91*
15 h	1873.6 ± 278.9	0.000*	685.73-2189.34*
18 h	1848.4 ± 212.7	0.000*	691.27-2194.78*
21 h	1792.7 ± 285.6	0.000*	701.39-2203.47*
24 h	1753.2 ± 251.8	0.000*	704.53-2207.02*
27 h	1728.4 ± 219.6	0.000*	841.75-2344.25*
30 h	1743.6 ± 231.9	0.000*	740.09-2242.58*
33 h	1706.3 ± 187.5	0.000*	841.98-2344.47*
36 h	1634.7 ± 196.8	0.000*	940.98-2443.47*
39 h	1642.4 ± 267.4	0.000*	873.56-2418.97*
42 h	1692.8 ± 156.7	0.000*	842.20-2344.69*
45 h	1683.6 ± 212.3	0.000*	859.67-2361.12*
48 h	1645.4 ± 179.3	0.000*	875.64-2378.14*

p and 95% CI values refer to comparison between each row's SVRI and the pre-infusion value. * statistically significant.

muscle of both peripheral and coronary vessels. It therefore results in coronary vasodilatation, improving the oxygenation of the heart and showing protective effects on the myocardium.[10,25]

The safety and effectiveness of levosimendan in the treatment of CF have been shown in several studies.[7-10,26-36] Moreover, patients treated with levosimendan experienced increased survival compared to those treated with dobutamine or placebo, a result that was maintained for 180 days.[7,9,36] Apart from improving cardiac performance and hemodynamics, it has been reported to exert a beneficial anti-inflammatory, antioxidant, and anti-apoptotic effect.[26-29,34,35] These immunomodulatory properties may contribute to improvement of cardiac contractile performance in CF patients. In addition, compared with dobutamine, it improves renal function in patients with acute decompensated heart failure.[37]

Interestingly, OR-1896, the active metabolite of levosimendan, has a long half-life of 70-80 hours and can be detected in circulation up to 2 weeks after discontinuation of a 24-hour infusion.[25] Beneficial effects on cardiac performance are sustained for at least 7 days after termination of a 24-hour infusion,[33] the postoperative period during which most cardiac complications occur. In agreement with this observation, ejection fraction was significantly elevated on the 7th postinfusion day in our patients.

Levosimendan treatment for the perioperative optimization of patients undergoing cardiac surgery has been reported in a few studies, with promising results in terms of safety and efficacy regarding cardiac performance, hemodynamics, intubation duration, and survival.[11-15] Ponschab et al also recently reported that preoperative levosimendan administration, starting a minimum of 2 hours before surgery, resulted in a significant increase in cardiac index and stroke volume index and a significant reduction in systemic vascular resistance index in elderly heart failure patients undergoing emergency hip fracture repair.[38] However, levosimendan has not been thoroughly evaluated in CF patients undergoing non-cardiac surgery.

Based on the aforementioned unique characteristics of the drug, we evaluated the effects of prophylactic preoperative levosimendan administration in CF patients undergoing elective non-cardiac surgery. Significant increases of ejection fraction, cardiac index, and stroke volume index, along with a substantial decrease of systemic vascular resistance index were identified. Levosimendan administration in a 24-hour continuous infusion resulted in beneficial improvement of patients' hemodynamics and cardiac performance, effects that were sustained for at least another 24 hours and, in the case of ejection fraction, 7 days. Moreover, no difference was noted between CIx, SVI, and SVRI values at the end of levosimendan infusion and the postoperative values. The finding that this optimization was sustained constantly throughout the intra- and immediate postoperative period, when surgical stress is greatest, may be of substantial importance. Furthermore, levosimendan infusion was well tolerated, with no adverse effects noted during the study period. No dose reduction or drug withdrawal was necessary. The postoperative period was uneventful in all patients and there was no perioperative morbidity or mortality during the 30 days follow up. In other studies, levosimendan has also been shown to significantly increase ejection fraction, cardiac index, stroke volume and cardiac output, and to decrease systemic vascular resistance, while not having a significant effect on heart rate and arterial pressure or causing arrhythmias.[9,11-15,31-34,36]

Hemodynamic monitoring of the study patients was performed via Swan-Ganz catheterization. It should be mentioned, though, that nowadays echocardiographic methods can be used as a valid alternative for the hemodynamic monitoring of heart failure patients, while invasive hemodynamic monitoring with right heart catheterization to guide treatment decisions in these patients may be hazardous and may lack prognostic value.[39]

Two of the study patients underwent major, high risk surgical procedures, two underwent moderate risk operations, and five patients had low surgical risk procedures. In addition, all cases but one were in NYHA functional class II. No differences regarding the obtained results were noted between these subgroups of patients, namely between patients with different NYHA classes or those having operative procedures of different surgical risk. However, the very small number of patients precludes any conclusions. Studies including adequate numbers of patients with worse functional status, as well as patients undergoing major, high risk surgery are therefore necessary to evaluate the safety and efficacy of prophylactic levosimendan treatment in such patients.

The results of this preliminary report imply that levosimendan, a novel positive inotropic agent, may have promising effects for the perioperative optimization of CF patients undergoing elective non-cardiac surgery, in terms of safety and efficacy. Our study, however, is limited by the small number of patients and the lack of a control group to exclude any poten-

tial effects of other factors other than the preoperative levosimendan administration. The findings of this series should thus be interpreted with great caution. Our results show that levosimendan can be safely administered to chronic heart failure patients undergoing non-cardiac surgery, while conclusions regarding its efficacy in these patients cannot be drawn. These data would support a randomized, controlled trial. Prophylactic preoperative levosimendan treatment in these patients, therefore, merits further study. Furthermore, since levosimendan seems to be a relatively expensive drug, studies aiming to define criteria as well as to specify which patients should be favored most by its administration appear to be warranted.

In conclusion, the preoperative optimization of heart failure patients undergoing elective non-cardiac surgery is of utmost importance; guidelines for the optimal perioperative management of these patients, however, have not been clarified. The current literature, although limited, implies that levosimendan may be a promising adjunct in our therapeutic repertoire for the treatment of such patients who are undergoing cardiac surgery, while this novel positive inotropic agent has not previously been evaluated in non-cardiac surgery. Our results imply that levosimendan may be safe and efficient for the perioperative optimization of heart failure patients undergoing elective non-cardiac surgery. Despite the small number of patients and the lack of a control group, we believe that the findings of this preliminary report appear promising and that the present study might open the way for further investigation regarding optimization of these patients. Furthermore, since the currently available data are limited, further prospective randomized placebo-controlled studies, including sufficient numbers of patients, are needed to confirm the perioperative cardioprotective benefit and safety of levosimendan and provide treatment recommendations. Sound clinical judgment, close perioperative monitoring, and an individualized therapeutic approach would be likely to reduce postoperative cardiac morbidity and mortality in this fragile group of patients.

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