

Levosimendan is superior to enoximone in refractory cardiogenic shock complicating acute myocardial infarction*

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Objective: Cardiogenic shock is the leading cause of death in patients hospitalized for acute myocardial infarction. The objectives were to investigate the effects of levosimendan, a novel inodilator, compared with the phosphodiesterase-III inhibitor enoximone in refractory cardiogenic shock complicating acute myocardial infarction, on top of current therapy.

Design: Prospective, randomized, controlled single-center clinical trial.

Setting: Medical and coronary intensive care unit in a university hospital.

Patients: Thirty-two patients with refractory cardiogenic shock for at least 2 hrs requiring additional therapy.

Interventions: Infusion of either levosimendan (12 μ g/kg over 10 min, followed by 0.1 μ g/kg/min over 50 min, and of 0.2 μ g/kg/min for the next 23 hrs) or enoximone (fractional loading dose of 0.5 mg/kg, followed by 2–10 μ g/kg/min continuously) after initiation of current therapy, always including revascularization, intra-aortic balloon pump counterpulsation, and inotropes.

Measurements and main results: Survival rate at 30 days was significantly higher in the levosimendan-treated group (69%, 11 of 16) compared with the enoximone group (37%, 6 of 16, $p = 0.023$). Invasive hemodynamic parameters during the first 48 hrs were comparable in both groups. Levosimendan induced a trend toward higher cardiac index, cardiac power index, left ventricular stroke work index, and mixed venous oxygen saturation. In addition, lower cumulative values for catecholamines at 72 hrs and for clinical signs of inflammation were seen in the levosimendan-treated patients. Multiple organ failure leading to death occurred exclusively in the enoximone group (4 of 16 patients).

Conclusions: In severe and refractory cardiogenic shock complicating acute myocardial infarction, levosimendan, added to current therapy, may contribute to improved survival compared with enoximone. (Crit Care Med 2008; 36:2257–2266)

KEY WORDS: cardiogenic shock; acute myocardial infarction; levosimendan; calcium sensitizer; enoximone; phosphodiesterase inhibitor

Cardiogenic shock (CS) is the leading cause of death in patients hospitalized for acute myocardial infarction (AMI) with mortality rates of up to 60% (1). Despite recent therapeutic advances, predominantly associated with early reperfusion strategies, CS continues to be associated with a dismal prognosis (2, 3). The syndrome of CS has been defined as the inability of the heart, as a result of impairment of its pumping function, to deliver sufficient blood flow to the tissues to

meet resting metabolic demands (4). The diagnosis is indicated by the combination of low mean arterial blood pressure, low cardiac index (CI), elevated pulmonary capillary occlusion pressure (PCOP), and an increase in systemic vascular resistance index (5). New evidence suggests that a systemic inflammatory response because of the release of inflammatory cytokines, the expression of inducible nitric oxide synthase, and inappropriate vasodilation may play an important role (6, 7).

Intra-aortic balloon pump counterpulsation and adjunctive medical therapy, using inotropic amines, are recommended in CS complicating AMI (5, 8–10). In the case of insufficient response, reflecting a refractory situation, phosphodiesterase-III inhibitors (PDEIs) may be advantageous (11). A different inotropic mode of action and additional vasodilating effects are mediated by PDEIs (12). Moreover, PDEIs have been shown to improve myocardial relaxation and coronary perfusion (12).

Levosimendan, a novel calcium-sensitizer and inodilator, affords positive ino-

tropic effects at therapeutic doses without an increase in cyclic adenosine monophosphate (cAMP) or intracellular calcium and, consequently, no increase in myocardial oxygen demand (13, 14). An improvement in myocardial perfusion as a result of vasodilatation, mediated by the opening of adenosine triphosphate-dependent potassium channels is available (15, 16). Moreover, persistent beneficial hemodynamic effects are due to the presence of a pharmacologically active metabolite with a prolonged elimination half-life (17). Levosimendan has been shown to improve hemodynamic function in patients with decompensated heart failure (18), even in addition to other inotropes (19), and seems to be safe in AMI (20). The purpose of the present study was to directly compare levosimendan with PDEIs on top of established therapy in patients with refractory CS complicating AMI.

METHODS

Patients. From April 2003 to July 2005 all patients admitted with AMI accompanied by

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hypotension and peripheral hypoperfusion were screened. AMI was defined by the presence of typical chest pain lasting 30 mins and an increase in troponin-T value or creatine kinase and CK-MB levels. An ST-segment elevation myocardial infarction needs typical criteria on 12-lead echocardiography (ST elevation >2 mm, Q-wave infarction, or a new left bundle-branch block). ST-segment elevation myocardial infarction and also non ST-segment elevation myocardial infarction were considered to be included. In all patients referred for percutaneous coronary intervention, an intra-aortic balloon pump (IABP) (Model 0684-00-0431-01, CS100, Datascope, Fairfield, NY or Model 05-840-LWS, AutoCat2Wave, Arrow International, Everett, MA) was inserted beforehand. Successful revascularization was determined as residual stenosis of <30% present in the artery responsible for infarction. To evaluate the left ventricular ejection fraction (LVEF) and any mechanical complications, a standard 2D-echocardiography (Sonos 5500 ultrasound system, Agilent Technologies, Andover, MA) was performed. The LVEF was calculated by Simpson's biplane method, as previously described (21).

The study protocol for this randomized, prospective, single-center open-label trial comparing levosimendan with enoximone on top of current therapy followed the principles of the Declaration of Helsinki of the World Medical Assembly and was approved by the Institutional Ethics Committee. Informed consent was obtained from each patient (whenever possible) or from the next of kin. Because of a planned interim analysis performed after recruiting 32 patients, we decided in consultation with the ethics committee to discontinue recruitment and terminate the study. This decision was made for ethical reasons, based on a clear trend toward reduced mortality for levosimendan.

Inclusion Criteria. Patients with refractory CS despite recommended current therapy (immediate revascularization, IABP support, optimal fluid status, and inotropes) within 2 hrs after percutaneous coronary intervention were included. Refractory CS was defined as (1) deteriorating hypotension as manifested by unaugmented systolic blood pressure below 90 mm Hg or requirement of inotropic amines and vasopressors to maintain unaugmented systolic blood pressure of at least 90 mm Hg, (2) a CI below 2.5 L/min/m², (3) a PCOP above 18 mm Hg, and (4) clinical signs of peripheral hypoperfusion (cold skin, mental confusion, or oliguria) (4, 22). Unaugmented blood pressure was measured after the IABP was turned off for 60 secs.

Exclusion Criteria. The exclusion criterion was hypotension related to any mechanical complications of AMI, such as ventricular septal rupture, cardiac tamponade, or acute severe ischemic mitral regurgitation. Additionally, patients with severe stenotic valvular disease, sustained ventricular tachycardia, ma-

jor bleeding, severe hepatic failure, severe systemic illness, or sepsis syndrome at the time of admission were excluded. All patients who had duration of CS longer than 24 hrs before arrival were excluded.

Treatment. All patients were treated in a cardiologic intensive care unit. Inotropes and vasopressors were titrated according to goal-directed therapy (for mean arterial blood pressure of at least 60 mm Hg and CI of at least 2.5 L/min/m²). Dosages at the time of randomization are given in Table 4. Intermittent intravenous fluid challenges were provided, if requested, to achieve appropriate filling pressures (PCOP). Patients meeting the inclusion criteria were randomly allocated to receive either levosimendan (Abbott Laboratories, Abbott Park, IL) or enoximone (Myogen GmbH, Bonn, Germany) using permuted block allocation with a block size of four (Fig. 1). Sequence generation for randomization was achieved using a sequence of random numbers from a computerized random-number generator. These blocks having equal numbers are used for the treatment groups, with the order of treatments within the block being randomly permuted. A random-number sequence was used to choose a particular block, which sets the allocation order for the subjects. Each possible permuted block is assigned a number. Using each number in the random number sequence in turn selects the next block, determining the next participant allocations. Similarly, the treatment group is allocated to the next patients in the order specified by the next randomly selected block. The treatment was assigned based on a 1:1 ratio. Enrollment was performed by the attending intensive care physician.

Levosimendan was administered with a front loading dose of 12 µg/kg over 10 min, followed by 0.1 µg/kg/min for 50 min, and of 0.2 µg/kg/min infused over the next 23 hrs. The doses administered were based on the results of previously published studies (11, 20, 23, 24). Enoximone was given with a fractional bolus administration of 0.5 µg/kg over 30 min and 2–10 µg/kg/min continuously, titrated to the best hemodynamic response. Catecholamines were selected according to our department guidelines, adapted to the current international guidelines for the management of AMI (9, 10, 25). This was in accordance with the European Society of Cardiology guidelines on the diagnosis and treatment of acute heart failure first published in 2005 (8). Single organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score of ≥3 for any organ system, and multiple organ failure (MOF) was defined as the simultaneous failure of two or more organs, other than cardiovascular failure.

Endpoints. The prespecified primary endpoint was all-cause mortality at 30 days. Secondary endpoints were changes in invasively measured hemodynamic variables during the first 48 hrs. Hemodynamic measurements

were routinely performed before administration of the study drug and at 2, 12, 24, and 48 hrs after starting the infusion. Arterial blood pressure measurements were performed continuously using an indwelling arterial cannula (Model Leader-Cath., VYGON, Norristown, PA) inserted into the radial artery. A pulmonary artery catheter (Model 774HF75, Edwards Lifesciences, Irvine, CA) was used to measure mean pulmonary artery pressure (MPAP), PCOP, and mixed venous oxygen saturation (Svo₂). Pressure values were read from the bedside patient monitoring system (Model Solar 8000, Marquette-Hellige Medical Systems, Milwaukee, WI) at end-expiration. Cardiac output measurements were performed using a continuous cardiac output monitoring set (Model VGS2V Vigilance, Edwards Lifesciences, Irvine, CA). Heart rate, heart-rhythm and oxygen saturation were also continuously recorded. We applied standard formulas for calculation of the CI, left ventricular stroke work index, systemic vascular resistance index, and pulmonary vascular resistance index. Cardiac power index (CPI) was determined by the following equation (26):

$$\text{CPI} = \left[\frac{\text{mean arterial pressure} \times \text{CO}}{451} \right] \times \text{body surface area}^{-1}$$

Statistical Analysis. The data are presented as medians and interquartile ranges (in square brackets) for continuous non-normally distributed data. Analysis of normality was performed with the graphic method of normal probability-quantile plot in combination with the Kolmogorov-Smirnov test. For the comparisons between non-normally distributed data, the Mann-Whitney U test was used. Selected data were presented with notched boxplots. All tests were two-sided and *p* values <0.05 were considered statistically significant. Multiple median test comparisons at different time-points were performed for each parameter separately and subjected to Bonferroni adjustment for correction of the type I error. In our analysis, five different time points were chosen. Cumulative survival was calculated by the Kaplan-Meier method and differences among groups were assessed by means of the log-rank test. Applying the Pocock stopping rule, for a study with a planned interim analysis, would assume a *p* value <0.029 as a stopping rule on the analysis of mortality for a treatment difference. On the basis of a two-sided test using a significance level of 0.029, a power of 80%, and a considered difference in mortality of 30%, it was anticipated that a minimum of 44 patients would need to be recruited in each group. Mortality rates in the levosimendan and enoximone groups were considered to be 50% vs. 80%. The statistical analysis was performed using Matlab software (The MathWorks, Natick, MA).

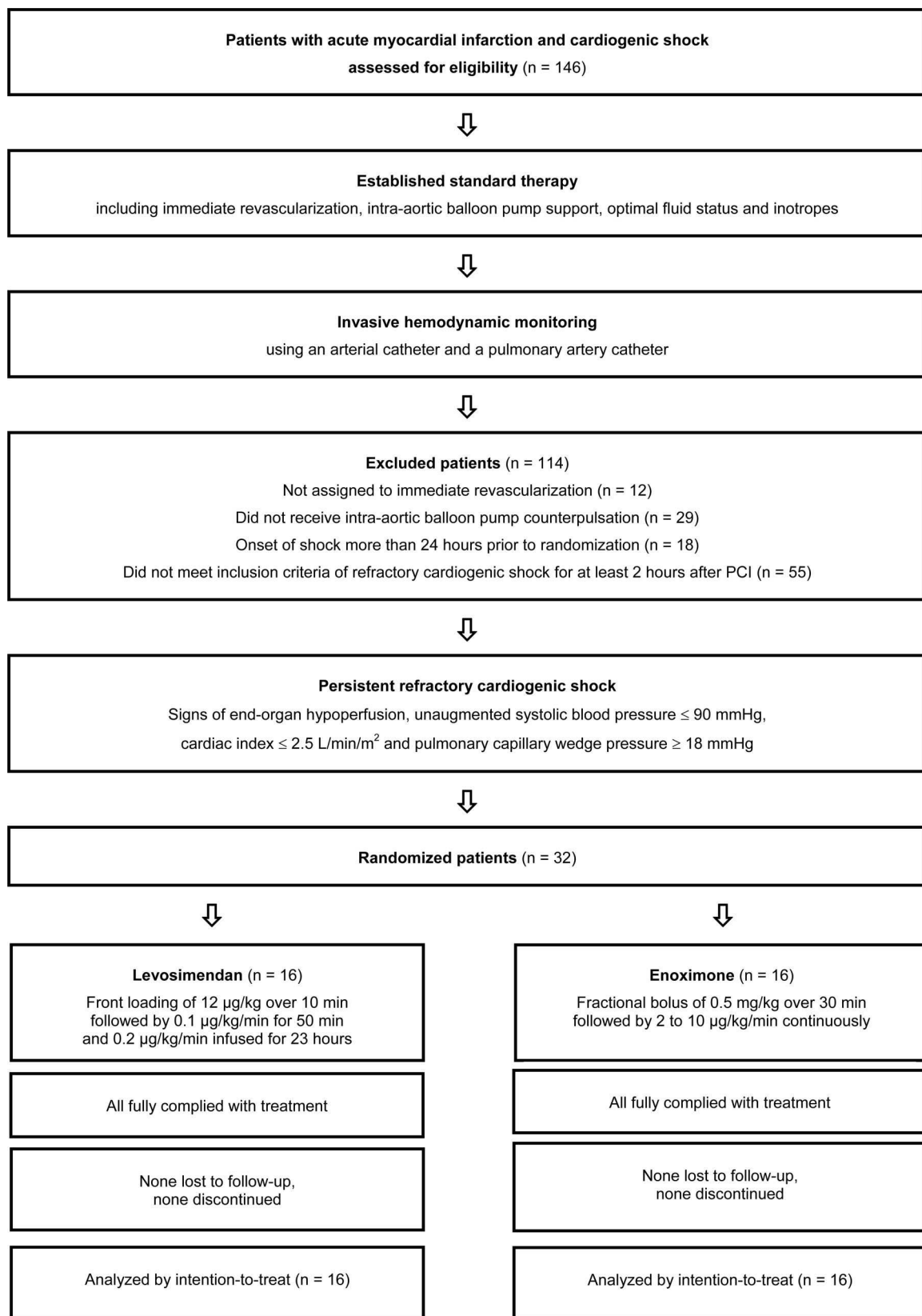


Figure 1. Overview of patient enrollment and trial profile.

Table 1. Baseline characteristics

| | Levosimendan (n = 16) | Enoximone (n = 16) | <i>p</i> |
|---|--------------------------|-----------------------|----------|
| Age (yrs) | 68 [60–70] | 68 [62–73] | 0.88 |
| Male gender, n (%) | 11 (69) | 9 (56) | 0.40 |
| Body mass index (kg/m ²) | 27 [26–29] | 28 [24–32] | 0.93 |
| Onset time of shock (hr) | 6.0 [4.0–8.0] | 7.0 [3.0–12.0] | 0.71 |
| Left ventricular ejection fraction (%) | 22 [18–31] | 27 [20–34] | 0.16 |
| Non-STEMI | 2 (12) | 3 (19) | 0.63 |
| Comorbidities ^a | | | |
| Diabetes mellitus, n (%) | 7 (44) | 5 (31) | 0.36 |
| Hypertension, n (%) | 14 (87) | 13 (81) | 0.63 |
| Hyperlipidemia, n (%) | 12 (75) | 11 (69) | 0.70 |
| Current smoking, n (%) | 8 (50) | 8 (50) | 1 |
| History of myocardial infarction, n (%) | 3 (19) | 5 (31) | 0.68 |
| History of previous cerebrovascular accident, n (%) | 1 (6) | 1 (6) | 1 |
| History of peripheral vascular disease, n (%) | 3 (19) | 1 (6) | 0.60 |
| History of vascular intervention, n (%) | 5 (31) | 2 (12) | 0.39 |

Values are median. Square parentheses denote interquartile range.

^aPatients may have more than one comorbidity.

Non-STEMI, non-ST segment elevation acute myocardial infarction.

Table 2. Treatment strategies and organ failure

| | Levosimendan (n = 16) | Enoximone (n = 16) | <i>p</i> |
|--|--------------------------|-----------------------|----------|
| Organ dysfunction and treatment before randomization | | | |
| CPR, n (%) | 10 (62) | 10 (62) | 1 |
| Out of hospital, n (%) | 6 (37) | 5 (31) | 0.71 |
| Lowest systolic blood pressure (mm Hg) | 83 [72–91] | 76 [69–88] | 0.11 |
| Highest lactate (mmol/L) | 5.5 [3.1–7.0] | 5.3 [2.5–8.4] | 0.66 |
| No. patients needing mechanical ventilation, n (%) | 9 (56) | 9 (56) | 1 |
| No. patients with new onset renal failure, n (%) | 1 (6) | 1 (6) | 1 |
| Administration of dobutamine, n (%) | 16 (100) | 16 (100) | 1 |
| Administration of norepinephrine, n (%) | 14 (87) | 14 (87) | 1 |
| Coronary catheterization findings and results of PCI | | | |
| Left coronary main as culprit lesion, n (%) | 3 (19) | 2 (12) | 0.63 |
| Coronary intervention, n (%) | 16 (100) | 16 (100) | 1 |
| Stent placed, n (%) | 15 (94) | 15 (94) | 1 |
| TIMI-III flow, n (%) | 14 (87) | 14 (87) | 1 |
| GP IIb/IIIa, n (%) | 8 (50) | 9 (56) | 0.72 |
| Median time to revascularization (hrs) | 8 [5–28] | 10 [7–34] | 0.78 |
| Multivessel intervention, n (%) | 5 (31) | 4 (25) | 0.69 |
| Development of organ failure and duration of treatment | | | |
| No. patients needing mechanical ventilation, n (%) | 13 (81) | 15 (94) | 0.29 |
| Mechanical ventilation (hrs) | 115 [31–220] | 172 [91–256] | 0.22 |
| Baseline GFR (mL/min/1.73 m ²) | 60 [52–73] | 63 [55–74] | 0.39 |
| No. patients with acute renal failure, n (%) | 5 (31) | 8 (50) | 0.28 |
| No. patients needing CRRT, n (%) | 5 (31) | 8 (50) | 0.28 |
| CRRT (hrs) | 101 [90–254] | 133 [61–512] | 0.68 |
| New onset atrial fibrillation, n (%) | 7 (44) | 9 (56) | 0.59 |
| Ventricular tachycardia or fibrillation, n (%) | 8 (50) | 11 (69) | 0.28 |
| Duration of IABP counterpulsation (hrs) | 71 [61–113] | 86 [41–126] | 0.78 |
| Stay on intensive care unit (days) | 10 [5–23] | 13 [7–19] | 0.79 |

Values are median. Square parentheses denote interquartile range.

CPR, cardiopulmonary resuscitation; TIMI, thrombolysis in myocardial infarction; GP IIb/IIIa, platelet glycoprotein IIb/IIIa receptor antagonist; GFR, glomerular filtration rate; CRRT, continuous renal replacement therapy; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention.

RESULTS

A total of 32 patients with refractory CS were randomized to enoximone or levosimendan as add-on to current therapy. The baseline characteristics are given in Table 1. Initial hemodynamic support, coronary catheterization, and percutaneous coronary intervention results are described in Table 2. No significant differences between the groups were observed for these parameters. Successful revascularization was obtained in all cases. A thrombolysis in myocardial infarction-III flow after percutaneous coronary intervention was established in 87% (14 of 16 patients) of both groups. All patients were treated with dobutamine and 14 of 16 patients in each treatment group received norepinephrine at the point of randomization. The enoximone infusion started at 3.5 [3.0–4.0] µg/kg/min and was given with a median duration of use of 5.1 [3.8–6.6] days.

Primary Endpoint. The 30-day overall survival rate was significantly higher in the levosimendan-treated group: 11 of 16 (68.7%) patients vs. 6 of 16 (37.5%) in the enoximone group (*p* = 0.023 log-rank test). The Kaplan-Meier survival curve is presented in Figure 2.

Hemodynamic Changes. Invasive hemodynamic and circulatory parameters are given in Table 3. A significant group difference in Svo₂ at 12 hrs was demonstrated, with higher values for the levosimendan group (Table 3). Despite the initial bolus administration in the levosimendan-treated group, a profound decrease in blood pressure was not observed (Fig. 3). Impressive increases were shown for CI, CPI, and left ventricular stroke work index, however, without relevant differences between the two groups. On the other hand, we observed a significant and persistent decrease in systemic vascular resistance index in all patients. Notably, the decrease in systemic vascular resistance index persisted in the levosimendan group despite discontinuation of the infusion after 24 hrs (Fig. 3). Favorable hemodynamic effects seem to be more pronounced in the levosimendan group during the first 12 hrs, especially for cardiac power index, CI (Fig. 3), left ventricular stroke work index, and Svo₂. However, the level of significance for a group difference was reached for Svo₂ only. Levosimendan-treated patients start at a higher baseline heart rate, suggesting a more unfavorable hemodynamic situation (Table 3).

Statistically significant differences in fluid administration during treatment were not observed, neither were differences in diuresis. In the administration of

catecholamines a relevant trend toward lower values in the levosimendan-treated patients over the course of time was evident (Table 4). In addition, cumulative

values for norepinephrine and dobutamine during the first 72 hrs showed a trend toward lower doses in the levosimendan-treated group (Fig. 4).

Organ Failure. The causes of death in the all-cause mortality rates at 30 days are given in Figure 5, which shows that the major cause of death was progressive and refractory heart failure as a result of mechanical pump failure of the infarcted myocardium. MOF occurred only in the PDEI group. MOF was responsible for death in 25% of patients (4 of 16) in the PDEI group only. The time of onset and duration of this MOF were quite different; the median time to beginning was 4.2 [1.3–6.8] days. The main reason for the development of multiple organ dysfunction syndrome and MOF was acute renal failure followed by respiratory failure. Hematologic, neurologic, and liver failure followed afterward. In line with these findings a relevant, but not significant, trend toward more renal failure and renal replacement therapy was seen in the PDEI group, despite equal baseline pa-

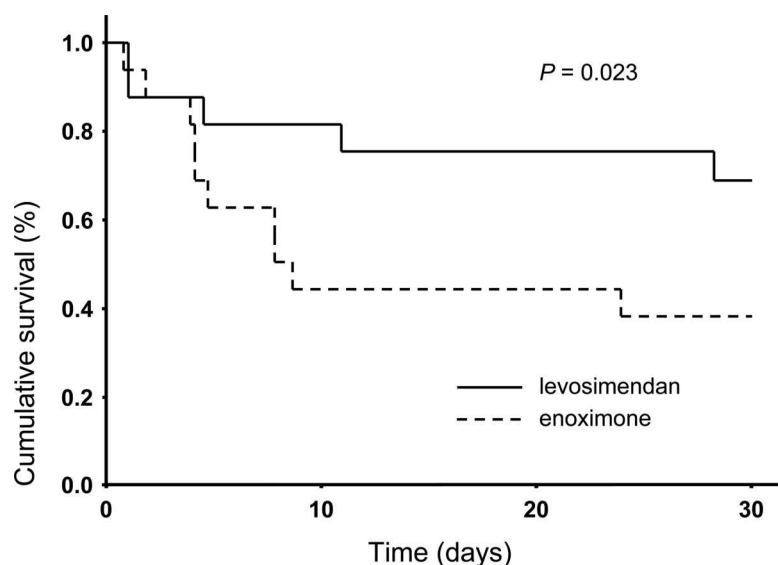


Figure 2. Kaplan-Meier analysis of the 30-day all-cause mortality rate in the levosimendan (solid line) and enoximone-treated groups (broken line), $p = 0.023$ (log-rank test).

Table 3. Changes in hemodynamics

| | Baseline (n = 36) | 2 hrs (n = 36) | 12 hrs (n = 36) | 24 hrs (n = 33) | 48 hrs (n = 32) |
|--|-------------------|------------------|-------------------------|------------------|------------------|
| Heart rate (beats per min) | | | | | |
| Levosimendan | 109 [100–120] | 113 [104–128] | 104 [95–121] | 104 [98–113] | 103 [98–107] |
| Enoximone | 101 [84–110] | 101 [82–114] | 102 [88–118] | 94 [86–115] | 101 [90–106] |
| PCOP (mm Hg) | | | | | |
| Levosimendan | 22 [18–24] | 19 [15–24] | 20 [14–25] | 19 [18–21] | 17 [16–20] |
| Enoximone | 20 [17–31] | 18 [14–22] | 20 [17–23] | 18 [15–24] | 21 [19–28] |
| MAP (mm Hg) | | | | | |
| Levosimendan | 72 [63–80] | 70 [64–80] | 65 [64–71] | 73 [67–77] | 75 [58–79] |
| Enoximone | 67 [60–77] | 62 [56–74] | 64 [58–69] | 68 [63–71] | 70 [63–83] |
| CI (L/min/m ²) | | | | | |
| Levosimendan | 2.3 [2.1–2.5] | 2.9 [2.5–3.4] | 3.0 [2.5–3.5] | 3.2 [2.7–3.2] | 3.1 [2.5–3.5] |
| Enoximone | 2.2 [1.7–2.4] | 2.7 [2.5–3.0] | 2.9 [2.5–3.2] | 3.2 [2.8–3.5] | 3.1 [2.8–3.3] |
| CPI (W/m ²) | | | | | |
| Levosimendan | 0.34 [0.31–0.43] | 0.46 [0.37–0.53] | 0.43 [0.39–0.55] | 0.50 [0.47–0.54] | 0.46 [0.38–0.60] |
| Enoximone | 0.30 [0.24–0.40] | 0.36 [0.32–0.47] | 0.38 [0.35–0.48] | 0.47 [0.40–0.55] | 0.49 [0.45–0.58] |
| LVS WI (gm/m ² /beat) | | | | | |
| Levosimendan | 13 [11–18] | 18 [12–20] | 18 [14–26] | 22 [16–24] | 20 [15–27] |
| Enoximone | 12 [10–19] | 16 [13–20] | 17 [16–21] | 19 [18–25] | 18 [15–30] |
| SVRI (dyne sec/cm ⁵ /m ²) | | | | | |
| Levosimendan | 2139 [1866–2447] | 1464 [1170–1848] | 1425 [1184–1769] | 1518 [1295–1708] | 1390 [1212–1574] |
| Enoximone | 1960 [1711–2345] | 1453 [1179–1611] | 1352 [1207–1615] | 1285 [1200–1541] | 1348 [1219–1852] |
| PVRI (dyne sec/cm ⁵ /m ²) | | | | | |
| Levosimendan | 369 [242–520] | 313 [233–371] | 218 [154–332] | 219 [187–260] | 255 [188–390] |
| Enoximone | 337 [204–455] | 307 [206–343] | 317 [164–369] | 201 [186–320] | 214 [157–217] |
| MPAP (mm Hg) | | | | | |
| Levosimendan | 31 [29–34] | 29 [27–35] | 27 [25–32] | 28 [22–32] | 29 [26–36] |
| Enoximone | 28 [27–40] | 28 [23–33] | 30 [27–35] | 30 [27–35] | 31 [26–37] |
| Svo ₂ (%) | | | | | |
| Levosimendan | 64 [57–71] | 68 [62–74] | 75 [64–78] ^a | 70 [66–75] | 68 [63–71] |
| Enoximone | 61 [50–66] | 69 [64–74] | 63 [60–71] | 69 [65–72] | 63 [60–69] |

Values are median. Square parentheses denote interquartile range.

PCOP, pulmonary capillary occlusion pressure; MAP, mean arterial blood pressure; CI, cardiac index; CPI, cardiac power index; LVS WI, left ventricular stroke work index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; MPAP, mean pulmonary artery pressure; Svo₂, mixed venous oxygen saturation.

^aSignificant difference between the two groups ($p = 0.01$).

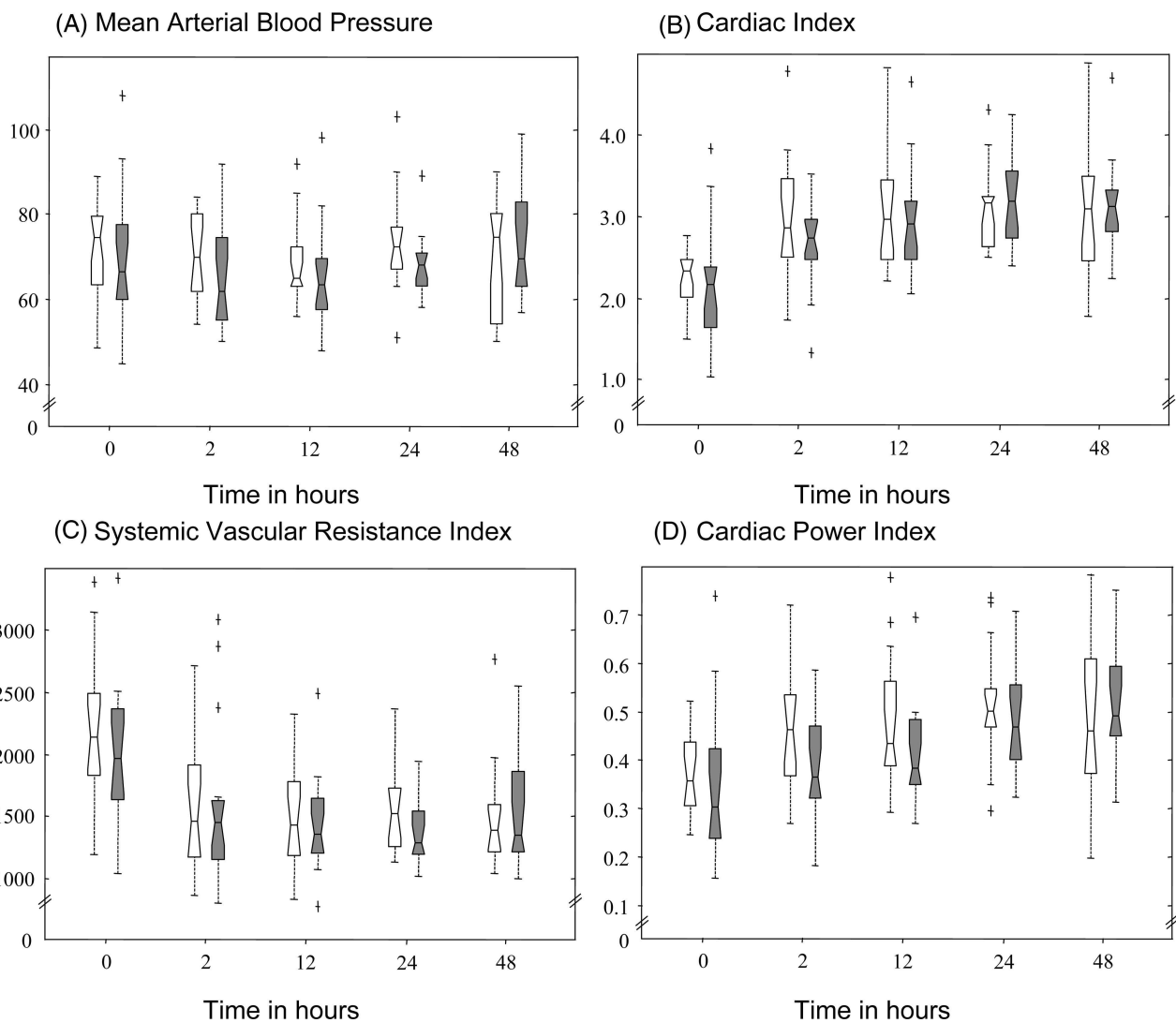


Figure 3. Hemodynamic changes during the first 48 hrs of treatment in both groups. *A*, mean arterial blood pressure (mm Hg); *B*, cardiac index (L/min/m²); *C*, systemic vascular resistance index (dyne sec/cm⁵/m²); *D*, cardiac power index (W/m²) in the levosimendan group (*white bars*) and the enoximone (*dark bars*) group. All values were nonsignificant for comparison between the two treatment arms.

Table 4. Hemodynamic support, fluid administration, and diuresis

| | Baseline (n = 36) | 2 hrs (n = 36) | 12 hrs (n = 36) | 24 hrs (n = 33) | 48 hrs (n = 32) |
|------------------------------|-------------------|-----------------------------|-----------------------------|----------------------------|-----------------------------|
| Dobutamine (μg/kg/min) | | | | | |
| Levosimendan | 9.3 [8.0–12.3] | 8.0 [5.8–11.3] ^a | 7.0 [4.0–11.3] ^a | 5.5 [3.8–8.0] ^a | 4.0 [2.3–11.0] ^a |
| Enoximone | 10.0 [8.8–14.0] | 12.0 [7.5–14.3] | 11.0 [7.5–13.6] | 11.0 [5.8–13.6] | 8.0 [4.3–11.8] |
| Norepinephrine (μg/kg/min) | | | | | |
| Levosimendan | 0.27 [0.13–0.40] | 0.20 [0.09–0.36] | 0.22 [0.02–0.44] | 0.15 [0.00–0.45] | 0.11 [0.05–0.42] |
| Enoximone | 0.24 [0.14–0.34] | 0.20 [0.09–0.49] | 0.27 [0.12–0.65] | 0.45 [0.08–0.79] | 0.50 [0.19–0.73] |
| Fluid administration (mL/hr) | | | | | |
| Levosimendan | 188 [144–250] | 200 [169–250] | 202 [173–270] | 181 [167–238] | 178 [133–195] |
| Enoximone | 225 [144–294] | 163 [125–281] | 186 [138–242] | 183 [148–237] | 179 [158–221] |
| Diuresis (mL/hr) | | | | | |
| Levosimendan | 90 [50–125] | 78 [45–100] | 60 [35–113] | 72 [34–110] | 113 [76–131] |
| Enoximone | 90 [49–185] | 70 [31–136] | 57 [35–102] | 62 [35–102] | 89 [57–116] |

Patients who did not receive norepinephrine were included in the calculation of the median dose. Values are median. Square parentheses denote interquartile range.

^aShows only a trend without significance between the two groups ($p = 0.04$).

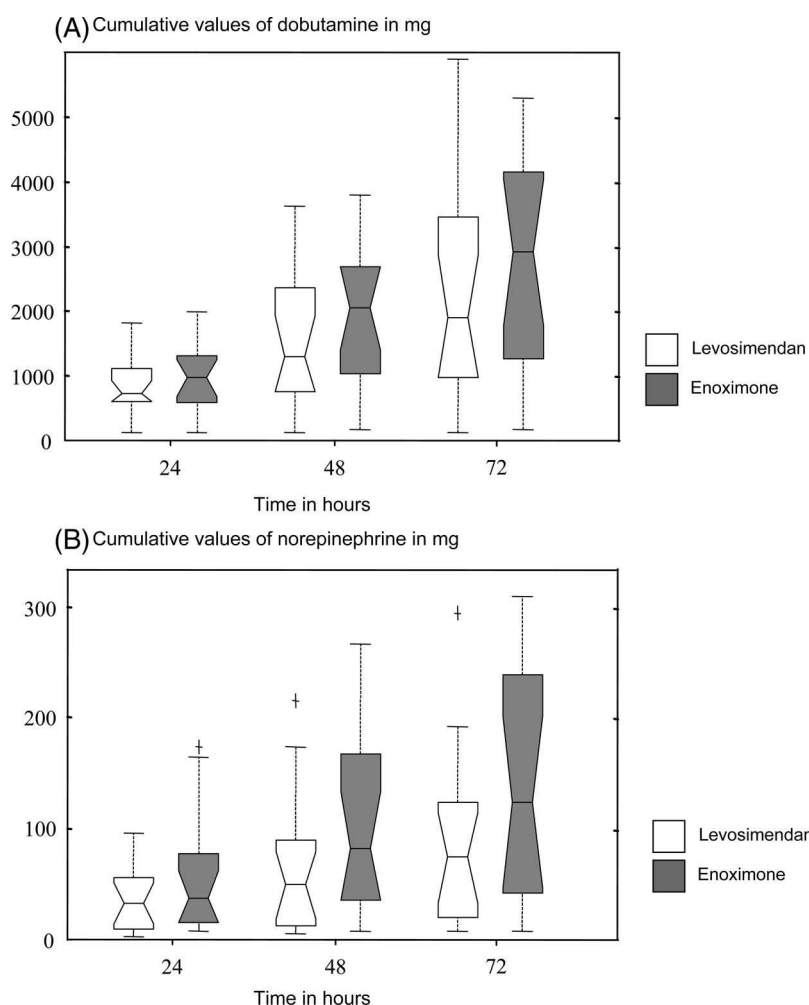


Figure 4. Cumulative values of dobutamine and norepinephrine during the first 72 hrs for the levosimendan group (white bars) and the enoximone group (dark bars). A, dobutamine (mg); B, norepinephrine (mg). All values were non-significant, †only a trend without significance for comparison between the two treatment arms ($p = 0.03$).

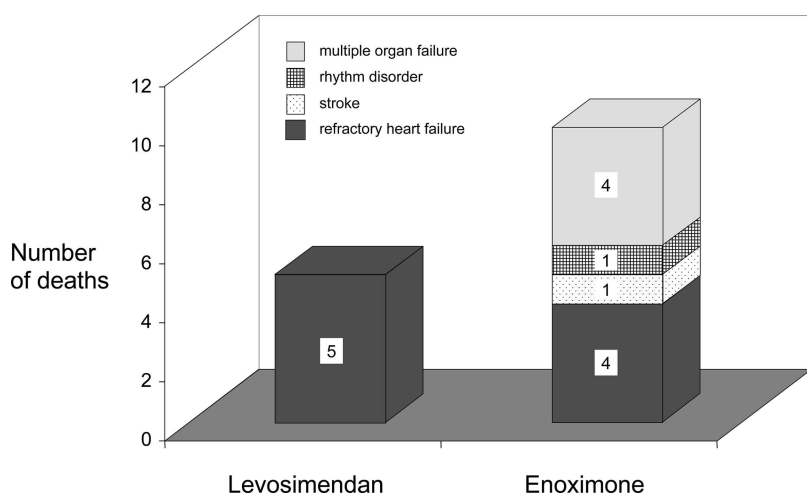


Figure 5. Bar graphs showing causes of death after 30 days in levosimendan- and enoximone-treated patients (refractory heart failure, stroke, rhythm disorder, and multiple organ failure).

rameters of renal function. Additionally, more patients required mechanical ventilation during therapy and also a longer duration of ventilation was observed in the enoximone-treated group. There were no significant differences in the onset of rate and rhythm disorders (Table 2).

Clinical signs of systemic inflammation, such as fever and elevated white blood cell count, were detected with a significant group difference at 24, 48, and 72 hrs, with higher values for the enoximone group. No differences in the values of C-reactive protein were found (Table 3). The number of patients who developed systemic inflammatory response differs in both groups. Early inflammatory response (during the first 48 hrs) occurred in eight levosimendan-treated patients and in 13 enoximone-treated patients. Signs of inflammation led routinely to a diagnosis of suspected sepsis. The confirmation of sepsis was obtained from blood culture results only; where no organisms were isolated, systemic inflammatory response was assumed. All patients were culture-negative at the time of evaluation.

Furthermore, in both groups infections developed over the course of time, but at a late point in the treatment, i.e., after 7 days in all cases. Pneumonia was the main reason for infection, diagnosed in seven levosimendan-treated patients and also in seven patients of the enoximone group. Additionally, two urinary infections were seen in the enoximone-treated patients. Sepsis occurred in three patients in the levosimendan group and in two patients treated with enoximone. The development of sepsis was not responsible for the MOF-related deaths in all these patients. Three of the four patients dying of MOF died during the first 4 days of treatment. No signs of infection were detected in the remaining patient.

A relevant trend toward lower values for the Simplified Acute Physiology Score II and for the SOFA score in the course of time was similar for levosimendan-treated patients, but statistically significant differences between the two treatment arms were not observed (Table 5).

DISCUSSION

The salient finding of the present study is a significant reduction in all-cause mortality rate at 30 days for patients with refractory CS complicating AMI by treatment with levosimendan on

Table 5. Laboratory markers of inflammation, Sequential Organ Failure Assessment (SOFA) score, and Simplified Acute Physiology Score (SAPS) II

| | Baseline (n = 36) | 24 hrs (n = 33) | 48 hrs (n = 32) | 72 hrs (n = 30) | 168 hrs (n = 27) |
|-------------------|-------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Fever (°C) | | | | | |
| Levosimendan | 36.8 [36.2–37.4] | 37.1 [36.0–37.9] | 37.5 [36.9–38.3] | 37.4 [36.9–38.1] | 37.8 [37.3–38.3] |
| Enoximone | 37.1 [36.2–37.5] | 38.4 [37.5–39.0] ^a | 38.3 [38.1–38.6] | 37.2 [36.7–38.1] | 38.4 [37.0–38.6] |
| WBC count (Gpt/L) | | | | | |
| Levosimendan | 13.5 [10.5–19.3] | 12.1 [8.4–14.5] | 9.5 [8.1–14.5] | 10.5 [8.0–11.9] | 10.2 [8.8–11.7] |
| Enoximone | 13.7 [12.3–19.3] | 14.3 [8.9–17.3] | 17.0 [13.5–17.9] ^a | 15.0 [12.6–17.5] ^a | 15.9 [10.2–19.9] ^b |
| CRP (mg/L) | | | | | |
| Levosimendan | 15 [3–70] | 91 [51–147] | 174 [139–187] | 200 [159–218] | 62 [44–82] |
| Enoximone | 39 [22–76] | 105 [72–198] | 179 [116–215] | 211 [163–235] | 66 [50–140] |
| SOFA score | | | | | |
| Levosimendan | | 11 [9–12] | 10 [9–12] | 10 [8–12] | 5 [3–12] |
| Enoximone | | 11 [11–13] | 13 [11–14] | 13 [11–14] | 11 [4–15] |
| SAPS II | | | | | |
| Levosimendan | | 61 [48–64] | 49 [42–61] | 45 [34–59] | n.a. |
| Enoximone | | 61 [53–71] | 58 [47–68] | 61 [45–69] | |

Values are median. Square parentheses denote interquartile range.

WBC, white blood cells; CRP, C-reactive protein; n.a., not available.

^aSignificant difference between the two groups ($p = 0.01$); ^bshows only a trend without significance between the two groups ($p = 0.02$).

top of current therapy compared with treatment with enoximone. Despite similar rates in death from cardiac origin, an MOF leading to death occurred in the enoximone group, exclusively. This positive effect was accompanied by a trend toward improved parameters of cardiac power index, CI, left ventricular stroke work index and SvO_2 during the first 12 hrs, reaching significance for SvO_2 only. Data for the use of levosimendan in CS are rare (27–29) and, to our knowledge, the present study shows the first direct clinical comparison of levosimendan vs. PDEI in these patients.

Established Therapy in CS. Despite immense improvement in treatment strategies, the prognosis of CS remains dismal (1, 3). Early reperfusion and IABP counterpulsation are strongly recommended (2, 8, 10). To stabilize impaired hemodynamics, vasoactive therapy (i.e., inotropic amines and vasopressors) is generally applied, in view of the lack of alternatives (23). Experimental and clinical evidence suggests that PDEIs might be advantageous in refractory heart failure and also in CS (11, 12). A benefit in mortality was not demonstrated, despite initial hemodynamic stabilization (23, 30). This might be explained by an increase in intracellular cAMP and intracellular calcium, potentially increasing myocardial oxygen demand (31).

Current Evidence for Levosimendan. Mainly three modes of action have been hypothesized as mediators of the positive effects of the calcium-sensitizer levosimendan: (1) positive inotropy, (2) an energy-sparing effect, and (3) also an anti-inflammatory effect.

The tendency to more improved hemodynamic measurements of levosimendan during the first 12 hrs, shown in this study, with a significant group difference for SvO_2 only, may indicate an earlier and much more balanced system of oxygen demand and delivery when compared with PDEI. The release of inotropy without an increase in oxygen demand (13, 14), favorable effects for relaxation (32), antistunning effects in myocardial tissue, and an improvement in myocardial perfusion (15) can be assumed to be causally determined. Furthermore, these effects may also be responsible for the lower incidence of early organ dysfunction in levosimendan-treated patients.

As shown in the present study, MOF occurred as a major cause of mortality in the PDEI group exclusively. More marked signs of inflammation during the first few days of therapy, such as fever and leukocytosis, suggest a more severe systemic inflammatory response to PDEIs (Table 5). This reaction could be responsible for the progression of initial multiple organ dysfunction syndrome into MOF. This part of the anti-inflammatory effects of levosimendan could be related to a superior improvement in hemodynamics, seen in our analysis as a trend only.

An additional explanation might be a disturbance in microvascular oxygen transport and consumption, promoting inflammatory response. As shown experimentally, levosimendan increases parameters of intestinal mucosal oxygenation more than milrinone and dobutamine, potentially with beneficial systemic effects (33). A direct improvement of regional perfusion in ad-

dition to the hemodynamic effects was also obtained clinically (34). Regional perfusion, shown directly as gastric mucosal perfusion by Doppler flow meter and also as a gradient between gastric mucosal and arterial P_{CO_2} , was increased by levosimendan when compared with dobutamine in patients with septic cardiac dysfunction. An increase in dobutamine dosing did not improve efficacy compared with levosimendan. In addition, renal function was improved, shown as an increase in urinary output and also in creatinine clearance. All these beneficial effects were obtained in patients with myocardial depression related to septic shock.

Furthermore, lesser clinical signs of inflammation might be related to reduced cumulative catecholamine values. This fact is seen in our analysis as a trend only, not reaching a level of significance in the course of time. Lower catecholamine values potentially reduce systemic inflammatory response, resulting in multiple organ dysfunction syndrome and ultimately in MOF.

In severe sepsis and septic shock cytokine release, leading to a massive systemic inflammatory reaction, has been shown to be responsible for development of MOF (35). Even in acute coronary syndromes an elevation of inflammatory markers and cytokines may indicate inflammatory response (36). These findings are independently associated with increased mortality (37). It is likely that similar mechanisms are operative in CS (38); however, clinical data are sparse (7, 39). Recently published data, with new insights to the pathophysiology of CS, are

in keeping with these results. The classic shock paradigm, only reflecting on inotropy, was supplemented by systemic inflammatory response as an important part of CS (6).

The activation of various cytokine cascades has been postulated to contribute to the refractoriness to inotropic drugs and to high mortality rates (7). Levosimendan may directly inhibit this activation of cytokines, as shown in severely decompensated heart failure (40, 41) and thus, potentially, the development of MOF. This effect may, in part, explain the advantageous effects of levosimendan.

Notably, in the levosimendan-treated patients no deaths because of MOF were observed, despite a high initial SOFA score, reflecting severe organ dysfunction. As we know, acute adverse hemodynamic effects of CS always result in potentially reversible multiple organ dysfunction syndrome. The development of the simplified acute physiology score II and the SOFA score in both groups over the course of time supports the hypothesis of an earlier and more severe systemic inflammatory response in the enoximone-treated group. As shown in Table 5, a trend toward lower simplified acute physiology score II and SOFA scores occurred in the levosimendan-treated patients without reaching significance in the first 7 days. This might be explained by a tendency toward much improved hemodynamic parameters and lower catecholamine values in levosimendan-treated patients.

Levosimendan has been shown to promote positive effects on mortality in acute heart failure after AMI (20) and in severe heart failure without AMI (42). In contrast, the recently published large multicenter trial SURVIVE failed to improve mortality in acute heart failure compared with dobutamine (24). However, the severity of heart failure may be quite different in these different patient populations and the occurrence of MOF and the systemic inflammatory response has not been identified. Noteworthy, all these studies excluded patients in CS. Therefore, we hypothesize that levosimendan may exert positive effects, predominantly in activation of inflammation in CS, resulting in systemic inflammatory response.

STUDY LIMITATIONS

This monocenter study includes a relatively small number of patients because

recruitment was stopped as a result of an interim analysis. This fact dropped the power of the present study because of the acceptance of a lower, but clinically relevant, difference between the treatment groups. However, this is a highly selective group of severely ill patients with refractory heart failure and CS in AMI. This study was enoximone-controlled because the severity of disease prohibited a placebo-controlled study. Moreover, repeated administration of levosimendan in refractory patients was not tested. Because of the open-label character of this study, a bias cannot be entirely excluded. Hence, we believe that interpretation of these results is limited. A larger, multicenter clinical trial of double-blind, randomized design will be needed to confirm these results.

CONCLUSIONS

According to our results, levosimendan would seem to be superior to enoximone as add-on therapy for patients with severe and refractory CS complicating AMI.

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