Levosimendan, a novel calcium sensitizer, binds calcium dependently to troponin C, thus improving systolic function without affecting diastolic function (1–4). This might be of clinical importance in patients with myocardial ischemia, where systolic dysfunction is usually combined with marked diastolic dysfunction. Chronically reduced perfusion (hibernating myocardium) or incomplete recovery from previous ischemic episodes (stunned myocardium) might be the underlying mechanism of diastolic dysfunction. The pathogenesis of myocardial stunning and chronic hibernation, which may be the result of repetitive episodes of stunning, has not been established. The major hypotheses are that it is caused by the generation of oxygen-derived free radicals and by a transient calcium overload on reperfusion. The radical and calcium hypotheses are likely to represent different facets of the same pathophysiologic cascade. However, the final lesion responsible for the contractile depression appears to be a decreased sensitivity of the myofibrils to calcium (5,6). Calcium sensitization might therefore directly improve the function of stunned myocardium (7).

The aims of the present study were to evaluate the effects of levosimendan on left ventricular (LV) systolic and diastolic function in patients in whom recanalization after an acute coronary syndrome (ACS) was angiographically proven or interventionally achieved.

However, levosimendan also acts as an opener of adenosine triphosphate–dependent potassium channels in vascular smooth muscle cells inducing vasodilatation (8,9). Thus, we chose to study the effect of levosimendan with LV pressure–volume relationships to aid in the differentiation of load alteration from direct myocardial effects.

**METHODS**

**Study patients.** Male and female patients with ACS (i.e., myocardial infarction [MI] or unstable angina; age 18 to 85 years) were enrolled. The diagnosis of MI was based on the presence of at least two of the following three criteria: a clinical history of ischemic-type chest discomfort, changes on serially obtained electrocardiographic tracings (for example, ST-segment elevation), and a rise in serum cardiac markers (elevated cardiac troponin levels, even in patients
coronary angiography.

Patients were ineligible if they had hemodynamically significant valvular or congenital heart disease; used inotropic drugs except digoxin and digitoxin within two days; had a body mass index $>32$ kg/m$^2$; had end-stage renal failure, liver cirrhosis, and clinically overt thyrotoxicosis; were treated with amiodipine or a class IC antiarrhythmic medication. This was a randomized, double-blinded, parallel group study assigning patients at a 2:1 ratio to levosimendan and placebo, respectively. The study followed the principles of the Declaration of Helsinki of the World Medical Assembly, with amendments. The protocol was accepted by the institutional ethical board, and informed consent was documented from each patient.

**Treatment regimens.** Ten minutes after successful coronary angioplasty, baseline measurement of pressures and volumes was performed, followed by intravenous infusion of 24 µg/kg levosimendan or placebo over 10 min. Twenty minutes after stopping the infusion, measurements were repeated.

**Methods of assessment.** Right and left heart pressures were measured by using a Swan Ganz or Cournand right heart catheter, as well as a Millar micromanometer-tipped pigtail catheter (Millar Instruments, Houston, Texas) for the LV. The cardiac index was calculated by applying the Fick principle. Left ventricular pressures were digitized every 0.005 s by means of the Cardis hemodynamic registration and evaluation system (Schwarzer, Munich, Germany). Left ventriculographic images were acquired at a rate of 25 frames/s in 30° right anterior oblique and 60° left anterior oblique projections, using the Philips Integris System (Philips Medical Systems, Hamburg, Germany). For evaluation of LV function, the DicomView program (Quazar, Hamburg, Germany) and a biplane LV analysis program (Pie Medical Imaging, Maastricht, The Netherlands) were used.

The LV endocardial contours were detected by an automated contour detection system and corrected manually, frame by frame. Left ventricular volumes were calculated by Simpson’s rule and corrected for body surface. Slager wall motion analysis was performed (10). Based on Slager wall motion analysis, the number of hypokinetic segments was counted (11).

End-diastolic and end-systolic volumes were determined from the LV angiogram as the largest or smallest LV volume, respectively, calculated from serial frames. The diastolic pressure closest to the beginning of the isovolumic contraction period in the differential plot of LV pressure was chosen as the end-diastolic pressure (12,13). The quotient of the end-diastolic pressure by the end-diastolic volume was chosen as the end-diastolic pressure/volume ratio. The end-systolic pressure/volume ratio resulted from the division of the end-systolic pressure by the end-systolic volume. Left ventricular pressure–volume loops were constructed by means of the plotting program Origin (Microcal Software, Northampton, Massachusetts). For the assessment of pressure–volume area, the pressure–volume loop was integrated.

The end-systolic pressure–volume relationship was estimated from a single cardiac beat by a method based on time-varying elastance curves. The time-varying elastance curves were generated from pressure–volume loops and normalized both by amplitude and time to peak amplitude. Pressure and volume data were measured at time $t_N$ (range 0.25 to 0.35; $P[t_N]$ and $V[t_N]$) and $t_{max}$ (time of end diastole to maximal pressure/volume ratio; $P[t_{max}]$ and $V[t_{max}]$).

The volume axis intercept $V_0$ was calculated by:

$$V_0 = \frac{P_N(t_N) V(t_{max}) - V(t_N) E_N(t_N)}{P_S(t_N) - E_N(t_N)}$$

and

$$E_{\text{max}} = \frac{P(t_{max})}{V(t_N) - V_0}$$

where $E_N(t_N)$ is the normalized elastance at time $t_N$ and $E_{\text{max}}$ is the normalized elastance at time $t_{max}$ (i.e., single-beat elastance). The single-beat elastance reflects the end-systolic pressure–volume relationship (i.e., acute inotropic change) (14).

The isovolumic relaxation period was defined as the period from maximum negative derivative of LV pressure to the time when pressure fell to 5 mm Hg above end-diastolic pressure of the following beat. The time constant of isovolumic LV pressure fall ($\tau$) was calculated from both the logarithm and derivative of pressure as:

$$\ln p = -\frac{1}{\tau} t + B$$

and

$$\frac{dp}{dt} = -\frac{1}{\tau} p + \frac{p_B}{T}$$

where $t$ is time in ms from maximal dP/dt; $B$ is the natural logarithm of LV pressure at maximal negative derivative of pressure; and $p_B$ is the baseline shift due to pleural or pericardial pressure (15,16).

**Statistical analysis.** All statistical analyses were done according to the intent-to-treat principle and were performed at a 0.05 level of significance. Demographic features and variables evaluating the systolic and diastolic function of stunned myocardium were summarized with descriptive statistics. The main direction of the shift in the pressure–
Table 1. Measurement of Hemodynamics and Systolic and Diastolic Function

<table>
<thead>
<tr>
<th></th>
<th>Levosimendan (n = 16)</th>
<th>Placebo (n = 8)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>20 min</td>
<td>Baseline</td>
</tr>
<tr>
<td>sPAP (mm Hg)</td>
<td>34.3 ± 2.2</td>
<td>32.6 ± 2.1</td>
<td>30.6 ± 2.6</td>
</tr>
<tr>
<td>dPAP (mm Hg)</td>
<td>13.3 ± 1.5</td>
<td>11.1 ± 1.2</td>
<td>11.6 ± 1.8</td>
</tr>
<tr>
<td>mPAP (mm Hg)</td>
<td>20.8 ± 1.8</td>
<td>17.9 ± 1.5</td>
<td>18.5 ± 2.1</td>
</tr>
<tr>
<td>mPCWP (mm Hg)</td>
<td>14.8 ± 1.5</td>
<td>10.6 ± 1.6</td>
<td>10.8 ± 1.6</td>
</tr>
<tr>
<td>sAoP (mm Hg)</td>
<td>136 ± 6</td>
<td>129 ± 7</td>
<td>131 ± 9</td>
</tr>
<tr>
<td>dAoP (mm Hg)</td>
<td>74 ± 3</td>
<td>72 ± 4</td>
<td>76 ± 5</td>
</tr>
<tr>
<td>mAoP (mm Hg)</td>
<td>97 ± 4</td>
<td>94 ± 4</td>
<td>97 ± 6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>109 ± 6</td>
<td>92 ± 6</td>
<td>92 ± 7</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>36 ± 6</td>
<td>27 ± 6</td>
<td>31 ± 4</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>2.2 ± 0.3</td>
<td>3.0 ± 0.6</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>LVPV area index (mm Hg ml per m²)</td>
<td>4,287 ± 478</td>
<td>3,843 ± 456</td>
<td>4,235 ± 857</td>
</tr>
<tr>
<td>CI (l/min per m²)</td>
<td>2.5 ± 0.2</td>
<td>2.5 ± 0.2</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>58 ± 3</td>
<td>67 ± 5</td>
<td>62 ± 4</td>
</tr>
<tr>
<td>Emax (mm Hg/ml)</td>
<td>2.3 ± 0.4</td>
<td>3.2 ± 0.7</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>18.2 ± 1.7</td>
<td>14.9 ± 1.9</td>
<td>17.6 ± 0.8</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>76 ± 6</td>
<td>67 ± 6</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>LVED P/V ratio (mm Hg/ml)</td>
<td>0.13 ± 0.01</td>
<td>0.12 ± 0.02</td>
<td>0.14 ± 0.02</td>
</tr>
<tr>
<td>Peak –dP/dt (mm Hg/s)</td>
<td>1,331 ± 82</td>
<td>1,356 ± 63</td>
<td>1,375 ± 80</td>
</tr>
<tr>
<td>τ90 (ms)</td>
<td>72 ± 5</td>
<td>57 ± 4</td>
<td>54 ± 6</td>
</tr>
<tr>
<td>τ10 (ms)</td>
<td>54 ± 4</td>
<td>45 ± 3</td>
<td>50 ± 4</td>
</tr>
</tbody>
</table>

Data are presented as the mean value ± SEM.

CI = cardiac index; dAoP = diastolic aortic pressure; dPAP = diastolic pulmonary artery pressure; E_max = single-beat elastance; HR = heart rate; LVED/V ratio = left ventricular end-diastolic pressure/volume ratio; LVEDP = left ventricular end-diastolic pressure; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVES/V ratio = left ventricular end-systolic pressure/volume ratio; LVESP = left ventricular end-systolic pressure; LVESVI = left ventricular end-systolic volume index; LVPV = left ventricular pressure-volume area index; mAoP = mean aortic pressure; mPAP = mean pulmonary artery pressure; LVEDVI = left ventricular end-systolic volume index; LVPV = left ventricular pressure-volume area index; mAoP = mean aortic pressure; mPAP = mean pulmonary artery pressure; mPCWP = mean pulmonary artery wedge pressure; Peak –dP/dt = maximum rate of fall of ventricular pressure; sAoP = systolic aortic pressure; sPAP = systolic pulmonary artery pressure; τ90 = index of early diastolic relaxation, calculated from the pressure derivative; τ10 = index of early diastolic relaxation, calculated by the logarithmic method.

volume loop from baseline to 20 min was compared between the two treatment groups using the Fisher exact test. Changes in other variables of interest were compared between the two treatment groups, using the nonparametric Cochran-Mantel-Haenszel test.

RESULTS

Twenty-four patients with an ACS, who were admitted to the intensive care unit, had diagnostic cardiac catheterization. Baseline clinical and demographic characteristics were similar among the patients (p > 0.3). The mean age of the patients was 60 years (range 37 to 84); their mean body weight was 80 kg (range 59 to 105); and their mean height was 172 cm (range 160 to 184). Seventeen male patients (5 placebo, 12 levosimendan) and seven female patients (3 placebo, 4 levosimendan) were included.

Twenty-four patients received aspirin (8 placebo, 16 levosimendan), 12 received ticlopidine (4 placebo, 8 levosimendan), 23 received heparin (8 placebo, 15 levosimendan), 21 received a beta-blocker (6 placebo, 15 levosimendan), 1 received calcium antagonists (levosimendan), 18 received angiotensin-converting enzyme inhibitors (4 placebo, 14 levosimendan), 3 received diuretics (levosimendan), and 4 received insulin (1 placebo, 3 levosimendan). Six patients (2 placebo, 4 levosimendan) had diabetes, and only one levosimendan-treated patient was taking oral hypoglycemics.

Fifteen patients received stents (4 placebo, 11 levosimendan), and eight patients underwent percutaneous transluminal coronary angioplasty (4 placebo, 4 levosimendan). Coronary angioplasty was not performed in one patient because of spontaneous restoration of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 and minimal coronary narrowing at the time of cardiac catheterization. Twenty-three patients had an acute MI. One patient had unstable angina due to chronic single-vessel disease of the left anterior descending coronary artery; all patients had chest pain at the time of study inclusion. Thirteen patients (5 placebo, 8 levosimendan) had anterior or lateral and 11 patients (3 placebo, 8 levosimendan) had inferior or posterior myocardial ischemia. The primary coronary status revealed TIMI flow grade 0 in 11 patients, grade 1 in 7 patients, grade 2 in 5 patients, and grade 3 in 1 patient (17).

After reopening of the infarct-related coronary artery, all patients reached TIMI flow grade 3. The postinterventional stenosis never exceeded 30%. Distributions of coronary flow rates and infarct location were similar in the levosimendan and placebo patients.

Hemodynamics recorded after coronary angioplasty (baseline), as compared with those recorded after levosimendan or placebo infusions (20 min), are shown in Table 1 and Figure 1. Although a slight decrease in mean aortic pressure and pulmonary artery pressure, as well as a considerable decrease in pulmonary capillary wedge pressure, was seen in the levosimendan-treated patients, small increases in these pressures were observed with placebo.
Influence on systolic function. The total number of hypokinetic segments decreased after levosimendan, from 8.9 ± 0.9 (mean ± SEM) to 6.5 ± 1.1, although it slightly increased after placebo, from 7.8 ± 1.0 to 8.5 ± 1.1 (p = 0.015).

End-systolic pressures and end-systolic volumes decreased with levosimendan and increased with placebo. The ejection fraction increased only with levosimendan, whereas the pressure–volume area decreased with levosimendan and increased with placebo. In addition, levosimendan significantly increased the single-beat elastance (Table 1, Fig. 1). An example of a pressure–volume loop is shown in a patient who received levosimendan (Fig. 2).

A leftward and/or upward shift of the systolic pressure–volume relationship, indicating improved systolic function, was observed in 8 of 16 patients treated with levosimendan and in one of eight patients who received placebo. However, the difference in frequency distribution between levosimendan and placebo was not significant (p = 0.178).

Influence on diastolic function. End-diastolic pressures and volumes decreased with levosimendan, although they were unchanged or increased with placebo. The end-diastolic pressure/volume ratio was unchanged (Table 1, Fig. 1). A downward and/or rightward shift of the diastolic part of the pressure–volume loop, indicating improved diastolic function, was observed in 5 of 16 levosimendan-treated patients and in five of eight placebo patients. An upward and/or leftward shift was observed in seven levosimendan patients and in one placebo patient. No shift was observed in four levosimendan patients or two placebo patients. It is noteworthy that the shifts were only minor and the difference in frequency distribution between levosimendan and placebo was not significant (p = 0.251). In addition, a true upward shift with levosimendan was observed in only one patient. In another patient, we found an...
upward shift of the early diastolic part of the pressure–volume loop, whereas in the late diastole it was unchanged. The index of early diastolic relaxation (τ), calculated from the pressure derivative and by the logarithmic method, decreased after levosimendan. The maximum rate of fall of ventricular pressure (peak \(-dP/dt\)) was unchanged by levosimendan (Table 1).

DISCUSSION

Influence on systolic function. The main finding of this study was that after a brief episode of severe ischemia, which was treated with percutaneous transluminal coronary angioplasty, overall and regional LV hypokinesia was improved in the presence of levosimendan, but not by angioplasty itself. In previous studies, a nitroprusside-induced reduction of elevated preload and afterload in acute MI resulted in improvement of global ventricular function, predominantly in noninfarcted LV segments (18,19). However, in our study, levosimendan reduced the number of hypokinetic segments, which suggests an effect of levosimendan beyond afterload reduction. In an experimental study in dogs, levosimendan improved regional contractile function of stunned myocardium after postischemic reperfusion (20).

In the present study, an increased ejection fraction, decrease in end-diastolic volume, increased single-beat elastance, and upward/leftward shift of the systolic part of the pressure–volume loop were observed, consistent with an improvement in systolic function. We anticipated an increase in the LV pressure–volume area, but rather observed a decrease. This later finding could be due to levosimendan also acting as an afterload-reducing agent. This interpretation is supported by previous studies (1–4,21,22).

As demonstrated by Colucci et al. (23), intracoronary administration of levosimendan might give additional information by excluding systemic vaso dilatation (i.e., afterload reduction). However, because of very limited data in acute MI, we conceded the systemic application to be safer and still a source of valuable clinical information (21,23).

In patients with congestive heart failure who were investigated with positron emission tomography, levosimendan did not show an increase in oxygen consumption, despite an increase in contractility (24,25). This finding is in contrast to the findings on other positive inotropic drugs like catecholamines and phosphodiesterase inhibitors (26–28). Levosimendan augments myocardial contractility by binding to troponin C and stabilizes the calcium-bound conformation of troponin C. The binding of calcium to troponin C is dependent on the intracellular calcium concentration (1–4). In the setting of ischemia, this mechanism distinguishes levosimendan from other positive inotropic drugs and might be of major importance.

Influence on diastolic function. However, calcium sensitization might have unfavorable effects on diastole. Nevertheless, studies in dogs and in muscle strips from failing human hearts demonstrated that levosimendan improved diastolic function (29,30). The changes in LV diastolic function after levosimendan in the present study were characterized by a leftward and/or upward shift of the diastolic pressure–volume curve and a decrease in both end-diastolic and end-systolic volume. These changes do not necessarily indicate improved diastolic function, but could be explained by the effects on systolic function due to positive inotropism and afterload reduction. However, the findings clearly exclude a deterioration of diastolic function. Furthermore, the early diastolic relaxation showed no impairment by levosimendan.

Hemodynamic effects. A decrease in both systemic and pulmonary artery pressures was observed. In a previous study, an increase of systolic arterial pressure was found 10 min after coronary angioplasty in patients with acute MI and without concomitant medical treatment. The mean pulmonary artery pressure remained unchanged. In our study, these findings were similar in patients who received placebo (31).

When administered to patients with congestive heart failure (averaged infusion rate at 6 h: 0.26 ± 0.08 μg/kg/min), levosimendan causes dose-related decreases in mean pulmonary capillary wedge pressure and mean pulmonary artery pressure. In addition, the mean arterial pressure was decreased. These hemodynamic effects appeared to be accompanied by improvement of symptoms and were not associated with a significant increase in the number of adverse events (21,22).

In our study, the hemodynamic effects in patients with acute MI were similar, and the drug was well tolerated.

Conclusions. In the setting of acute ischemic heart disease, levosimendan improved the function of stunned myocardium, without obvious impairment of diastolic function.

REFERENCES