

BASIC PHARMACOLOGY

Effect of the Calcium Sensitizer Levosimendan on the Performance of Ischaemic Myocardium in Anaesthetised Pigs

Peter Tassani¹, Hubert Schad², Werner Heimisch²,
Angelika Bernhard-Abt², Ursula Ettner²,
Nikolaus Mendler², and Rüdiger Lange²

¹Department of Anaesthesiology and; ²Department of
Cardiovascular Surgery, German Heart Centre Munich,
Lazarettstr 36, D-80636 München, Germany

Summary. The calcium sensitizer levosimendan (LEV) improves the function of stunned myocardium, cardiac performance in heart failure, and possibly the efficiency of myocardial work. The present experiments investigated the effect of LEV on myocardial contraction and metabolism of acutely ischaemic myocardium distal to a functionally effective coronary artery stenosis. Anaesthetised open chest pigs ($n = 14$) were instrumented to assess heart rate (HR), aortic pressure (AoP), cardiac output (CO), blood flow in the left descending (QLAD) and circumflex (QLCX) coronary artery, myocardial end-diastolic segment length and systolic shortening (edL, MSS by sonomicrometry) in the LAD- and LCX-territory. Systemic vascular resistance (SVR), and a myocardial power index (PowI) for the LAD- and LCX-region were calculated. Following obstruction of QLAD by an external snare proximal to the first diagonal branch LEV was given intravenously (10 + 20 + 30 $\mu\text{g}/\text{kg}$ 15 min apart, $n = 8$) or the vehicle of LEV ($n = 6$). Following LEV haemodynamics and regional myocardial performance changed significantly: HR +22 min^{-1} , AoP -6 mmHg, CO +17%, SVR -21%; intact myocardium: QLCX +15%, RLCX -24%, PowILCX +39%; ischaemic myocardium: QLAD -7%, MSSLAD -42%, PowILAD -27%. The data confirm the pharmacological profile of LEV: positive chronotropy, positive inotropy, and vasodilatation. The pump function of acutely ischaemic myocardium worsened following LEV. The efficiency of myocardial performance did not improve. A beneficial effect of LEV on the function of ischaemic myocardium was possibly outmanoeuvred by the increase in heart rate.

Key Words. calcium sensitizer, levosimendan, anaesthetised pigs, ischaemic myocardium, myocardial function

Introduction

Levosimendan has been shown to augment myocardial contractility by binding to troponin C during the contraction phase of the cardiac cycle and thereby sensitizes heart muscle to calcium without altering intracellular Ca^{2+} concentration [1]. In contrast, the currently used intravenous drugs to treat decompensated heart failure, including phosphodiesterase inhibitors and

catecholamines improve cardiac pump function by increasing calcium levels in the myocardial cells. As such, these drugs may produce arrhythmia and worsen the cardiac oxygen balance [2,3]. Indeed, levosimendan also inhibits cardiac and vascular smooth muscle phosphodiesterase [2,3]. This effect, however, is apparent only at larger doses and less pronounced when compared to pure phosphodiesterase inhibitors.

The positive inotropic effect of levosimendan was demonstrated for intact myocardium [4,5] and for muscle strips from human hearts with end-stage cardiomyopathy [6]. Reduced regional contractility in the case of stunned myocardium could be improved by intracoronary levosimendan in dogs [7]. In patients with acute myocardial infarction and stunned myocardium the ventricular function was improved by levosimendan compared to placebo [8]. Levosimendan is less likely to induce the above mentioned adverse effects of usually used inotropic drugs. Treatment of decompensated heart failure with i.v. dobutamine or levosimendan resulted in a lower risk of major adverse clinical events following levosimendan as compared to dobutamine [9].

Patients with unstable angina referred for emergency coronary artery surgery or interventional procedures in the cardiac catheterisation laboratory often develop low-output status requiring positive inotropic support. Calcium sensitizers may be superior to other positive inotropic drugs to treat these patients, because calcium sensitizers possibly improve the balance of myocardial oxygen demand and mechanical work as shown for another calcium sensitising drug (EMD 60263) in isolated rabbit hearts [10]. Data on the effects of levosimendan on performance and metabolism of ischaemic myocardium are not available yet.

Address for correspondence: Peter Tassani, Department of Anaesthesiology, German Heart Centre Munich, Lazarettstr 36, D-80636 München, Germany. Tel.: +49 89 1218 4611; Fax: +49 89 1218 4613; E-mail: tassani@dhm.mhn.de

The aim of the present investigation was therefore to study effects of intravenous application of levosimendan on the mechanical function and the metabolic status of acutely hypoperfused myocardium in a well controlled animal model.

Material and Methods

The experiments were approved by the Regierung von Oberbayern (reference number 211-2531-50/98). The animals have received human care in compliance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication 85-23).

Animals and anaesthesia

The experiments were performed in 14 domestic pigs of either sex, body weight (BW) 27–50 kg. The animals were pre-treated with azaperon i.m. (4 mg/kg Stresnil[®], Janssen, Neuss, FRG), ketamine i.m. (5 mg/kg Ketanest[®], Parke Davis, München, FRG), and atropine sulfate i.m. (25 µg/kg, Braun, Melsungen, FRG). Anaesthesia was induced by i.v. thiopental sodium (12.5 mg/kg, Trapanal[®], Byk-Gulden, Konstanz, FRG) and sufentanil (30 µg/kg Sufenta[®], Janssen-Cilag, Neuss, FRG) and maintained by i.v. midazolam-sufentanil (0.1 mg/kg/h Midazolam-ratiopharm[®], Ratiopharm, Ulm, FRG, and 1.25 µg/kg/h Sufenta[®]). The animals were paralysed by pancuronium bromide i.v. (priming 0.1 mg/kg, sustaining dose 4 µg/kg/min Pancuronium Curamed[®], Curamed, Karlsruhe, FRG) and ventilated with O₂/N₂O = 1:1 via an endotracheal tube. Arterial pCO₂, pO₂, base excess, and K⁺ were measured every 30 min (GEMPremier 5300, Mallinckrodt Sensor systems, Ann Arbor, MI). pCO₂ was adjusted to 35–40 mmHg and pO₂ to >100 mmHg by ventilation, base excess was kept at ±2 mmol/l by NaHCO₃ or HCl, and plasma K⁺ at 4.5–5.5 mmol/l by i.v. K-Mg-aspartate (Inzolen[®], Köhler, Alsbach, FRG). Rectal temperature was monitored by a thermistor (9230-20, Ellab, Rødvre, Denmark) and kept at 36.5–38.5°C.

Preparation and instrumentation (Fig. 1(A))

Jugular veins and a femoral artery were cannulated. The heart was exposed from a left side thoracotomy and suspended in a pericardial cradle. Catheters were placed in the left atrium and in the pulmonary artery; catheter tip manometers were advanced to the ascending aorta from a femoral artery (SPC 350, Millar, Houston, USA) and to the left ventricle from the left atrial appendage (SRP 524, Millar). Perivascular ultrasonic transit-time flowprobes (T206, Transonic, Ithaca, USA) were attached to the ascending aorta, left anterior descending and circumflex coronary artery (LAD, LCX). A tourniquet was placed around the LAD distal to the flow probe. Ultrasonic micro probes for analysis of regional ventricular wall movement were placed intramyocardially in the LAD- and LCX-territory. An

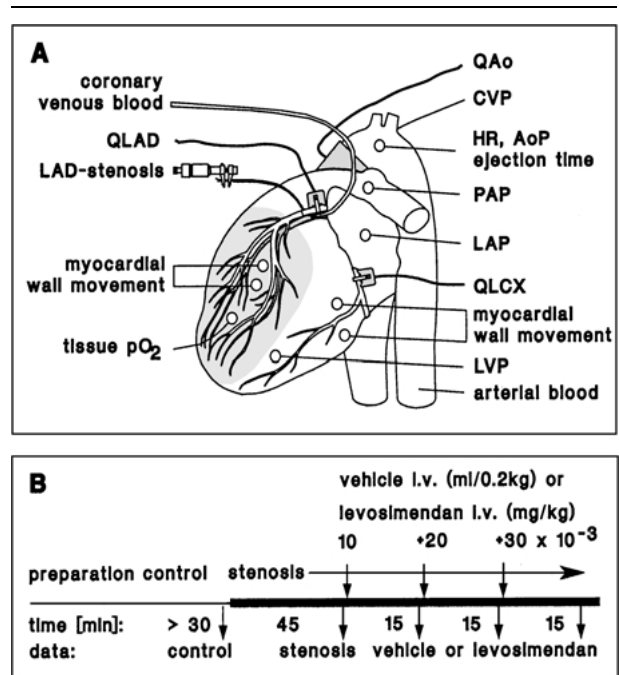


Fig. 1. Instrumentation of the animals (A) and experimental protocol (B). QLAD: left descending coronary artery blood flow; Qao: aortic blood flow; CVP: central venous pressure; HR: heart rate; AoP: aortic blood pressure; PAP: pulmonary artery pressure; LAP: left atrial pressure; LVP: left ventricular pressure QLCX: left circumflex coronary artery blood flow; pO₂: oxygen partial pressure.

oxygen sensing catheter microprobe (LICOX[®], GMS, Mielkendorf, FRG) was introduced into the myocardium supplied by the LAD. A teflon cannula (26G) connected to a silastic tube was placed in the proximal great cardiac vein. Pericardium and chest remained open throughout the experiment.

Biosignal monitoring, blood and tissue analyses

The following parameters were monitored: heart rate (HR), central venous pressure (CVP, P23ID, Spectramed, Oxnard, USA), pulmonary artery pressure (PAP; P23ID, Spectramed, Oxnard, USA), left atrial pressure (LAP; P23ID, Spectramed, Oxnard, USA), left ventricular end-diastolic pressure (LVedP), left ventricular dP/dt_{max} & dP/dt_{min}, aortic pressure (AoP), aortic blood flow (QAo), coronary artery blood flow (QLAD, LCX), myocardial oxygen pressure (ptO₂), cyclic length changes of myocardial wall segments in the LAD- and LCX-territory by sonomicrometry as described in detail previously [11], and airway pressure (P23ID, Spectramed, Oxnard, USA).

Aortic (a) and coronary venous (cv) blood samples were analysed for oxygen saturation (SO₂, GEMPremier 5300, Mallinckrodt Sensor systems, Ann Arbor, USA), haemoglobin (Hb; Cyan-Hb, Roche,

Mannheim, FRG), and lactate (Lac; lactate oxidase/ peroxidase, Sigma Diagnostics, Taufkirchen, FRG).

Post mortem, the myocardial areas where the ultrasonic microprobes were implanted, were stained with triphenyl tetrazolium chloride to look for myocardial infarction. None of the experiments showed myocardial infarction.

Experimental protocol (Fig. 1(B))

After sampling of control data, Q_{LAD} was obstructed by the tourniquet within 10 min to reduce myocardial systolic shortening distal to the stenosis to about 50% of control. This hypoperfusion was maintained to the end of the experiment. A period of >30 min were allowed for haemodynamic stabilisation before stenosis data were assessed followed by intravenous bolus injection of either the vehicle of levosimendan ($n = 6$) (see below) or levosimendan ($n = 8$). Identical volumes of vehicle and levosimendan were injected in 15 min intervals (50, 100 and 150 $\mu\text{l} \cdot \text{kg}^{-1}$), the dosage of levosimendan was 10 + 20 + 30 $\mu\text{g}/\text{kg}$. Haemodynamic data and blood samples were taken 14 min after each bolus of levosimendan (Fig. 1(B)).

The experiments were terminated by i.v. 30 mg/kg thiopental sodium (Trapanal[®], Byk-Gulden, Konstanz, FRG) and subsequent injection of 20 mval KCl into the left ventricle.

Preparation of levosimendan

Levosimendan (LEV) was kindly supplied as powder by Orion Pharma, Espoo, Finland. LEV solution was prepared as described previously [7]. The dry substance (10 mg) was dissolved in pure ethanol (12.5 ml; Sigma-Aldrich, Taufkirchen, FRG), and diluted by polyethylenglycol (12.5 ml; Sigma-Aldrich, Taufkirchen, FRG) and 0.9% NaCl (25 ml), yielding a final concentration of 200 $\mu\text{g}/\text{ml}$.

Data assessment, calculations, statistical analysis

The haemodynamic analogue signals and the respiratory pressure were recorded on multi-channel chart recorders (TA 5000, Gould, Valley View, USA). The haemodynamic variables were read in end-expiration. The following calculations were performed:

- aortic blood flow was normalised by the body weight (BW) and is given as cardiac output $\text{CO} = Q_{Ao}/\text{BW}$ [$\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$]
- systemic vascular resistance $\text{SVR} = (\text{AoP} - \text{CVP})/\text{CO}$ [$\text{mmHg} \cdot \text{min} \cdot \text{kg} \cdot \text{ml}^{-1}$]
- pulmonary vascular resistance $\text{PVR} = (\text{PAP} - \text{LAP})/\text{CO}$ [$\text{mmHg} \cdot \text{min} \cdot \text{kg} \cdot \text{ml}^{-1}$]
- coronary vascular resistance $\text{R}_{\text{cor}} = (\text{AoP} - \text{CVP})/Q_{\text{cor}}$ [$\text{mmHg} \cdot \text{min} \cdot \text{ml}^{-1}$]
- fractional myocardial systolic shortening $\text{fMSS} = (\text{MSS}/\text{edL}) \cdot 100$ [%] (with myocardial systolic shortening MSS and end-diastolic myocardial segment length edL)

- regional myocardial power index $\text{PowI} = \text{fMSS} \cdot \text{Pej} \cdot \text{HR}/\text{tej}$ (with mean aortic pressure during ejection Pej and duration of ejection tej; control data were set as 100%)
- myocardial oxygen uptake $\text{MVO}_2 = (\text{SO}_{2a} - \text{SO}_{2cv}) \cdot \text{Hb} \cdot 1.34 \cdot Q_{LAD}$ [$\text{ml} \cdot \text{min}^{-1}$]
- myocardial lactate uptake $\text{MLac} = (\text{Lac}_a - \text{Lac}_{cv}) \cdot Q_{LAD}$ [$\text{mg} \cdot \text{min}^{-1}$]

The data are given as mean \pm SEM. The data were subjected to the Friedman two-way ANOVA and Wilcoxon matched-pairs signed-ranks test using the statistic software SPSS[®] 10.0 for Windows[™]. Significance of differences stenosis vs control, levosimendan vs stenosis, and vehicle vs stenosis was accepted for a two tailed $p < 0.05$.

Results

LAD stenosis (Tables 1 and 2)

LAD blood flow was reduced by about 37% by the external constriction of the vessel. This myocardial hypoperfusion caused a decrease in systolic shortening and regional myocardial power index (fMSS_{LAD} : -51%; MPI_{LAD} : -41%). Myocardial end-diastolic segment length was increased (edL_{LAD} : +7.4%) following LAD stenosis. The myocardial oxygen pressure in the LAD-area was decreased from 66 to 22 [mmHg], myocardial uptake of lactate (0.64 mg/min) turned into lactate release (1.74 mg/min). Myocardial oxygen uptake of the LAD-area was reduced in 5 experiments, unchanged in 2 experiments, and increased in 1 experiment following LAD-stenosis. Thus, the mean change did not reach the level of statistical significance.

In the non-ischaemic LCX-area, systolic shortening, myocardial power index and LCX blood flow showed a significant increase following LAD stenosis. End-diastolic segment length was not changed significantly.

Global haemodynamics remained nearly unaffected by the LAD-stenosis. Significant changes were observed for heart rate (+11 beats/min), for left ventricular end-diastolic pressure (LVedP: +6.0 mmHg), and for mean pulmonary artery pressure (PAP: +2.8 mmHg). Aortic pressure, central venous pressure, cardiac output, dP/dt_{max} , dP/dt_{min} , pulmonary vascular resistance and systemic vascular resistance did not change significantly following LAD-stenosis.

Vehicle

The intravenous application of the vehicle of levosimendan was not associated with major changes of regional myocardial performance and global hemodynamics. Following the third dose of vehicle as compared to the data before vehicle heart rate was increased (HR: +4 beats/min), pulmonary vascular resistance was higher (PVR: +19%), LAD vascular resistance was decreased (R_{LAD} : -8%), and end-diastolic length and systolic shortening of the myocardial segments in the LCX-area were reduced (edL_{LCX} : -2.5%;

Table 1. Global haemodynamic data from anaesthetised, open chest pigs before (control) and during (stenosis) reduced left descending coronary artery blood flow by an external stenosis, and following subsequent intravenous application of levosimendan 10 + 20 + 30 $\mu\text{g} \cdot \text{kg}^{-1}$ (Lev10, 20, 30) during maintained stenosis

	Control	Stenosis	Lev10	Lev20	Lev30
HR	76 ± 5	87 ± 8*	93 ± 9 [†]	100 ± 9 [†]	109 ± 9 [†]
AoPm	85 ± 3	85 ± 4	82 ± 4	80 ± 5 [†]	79 ± 5 [†]
CVP	6.0 ± 0.5	7.1 ± 1.1	6.2 ± 1.0 [†]	5.6 ± 1.1 [†]	5.1 ± 1.1 [†]
PAP	19.3 ± 1.3	22.1 ± 1.4*	21.9 ± 1.5	22.4 ± 1.7	22.3 ± 1.5
LVedP	15.1 ± 2.1	21.1 ± 2.8*	20.0 ± 3.0	19.6 ± 3.4	17.3 ± 3.4 [†]
CO	97 ± 10	92 ± 6	96 ± 6	99 ± 7	108 ± 6 [†]
dP/dt _{max}	1566 ± 185	1463 ± 124	1548 ± 118	1597 ± 132 [†]	1768 ± 141 [†]
dP/dt _{min}	1369 ± 210	1252 ± 170	1229 ± 152	1202 ± 147	1269 ± 153
PVR	12.2 ± 1.2	12.0 ± 0.9	11.8 ± 1.0	12.3 ± 1.3	12.1 ± 1.3
SVR	84 ± 6	86 ± 5	79 ± 5 [†]	74 ± 4 [†]	68 ± 4 [†]

Mean ± SEM ($n = 8$); $2p < 0.05$, *stenosis vs control, [†]Lev vs stenosis.

HR = heart rate [min^{-1}]; AoPm = mean aortic pressure [mmHg]; CVP = central venous pressure [mmHg]; PAP = pulmonary artery pressure [mmHg]; LVedP = left ventricular enddiastolic pressure [mmHg]; CO = cardiac output [$\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$]; dP/dt_{max,min} = maximal velocity of rise and fall in left ventricular pressure [$\text{mmHg} \cdot \text{s}^{-1}$]; PVR, SVR = pulmonary and systemic vascular resistance [$\text{mmHg} \cdot \text{min} \cdot \text{kg} \cdot \text{ml}^{-1}$].

Table 2. Data on left circumflex (LCX) and left anterior descending (LAD) coronary artery area from anaesthetized, open chest pigs before (control) and during (stenosis) reduced LAD blood flow, and following subsequent intravenous application of levosimendan 10 + 20 + 30 $\mu\text{g} \cdot \text{kg}^{-1}$ (Lev10, 20, 30) during maintained stenosis

	Control	Stenosis	Lev10	Lev20	Lev30
LCX					
Q	24.4 ± 4.4	27.8 ± 5.2*	29.3 ± 5.4	29.4 ± 5.3	32.0 ± 4.9 [†]
R	3.7 ± 0.5	3.4 ± 0.6	3.1 ± 0.5 [†]	3.0 ± 0.5 [†]	2.6 ± 0.4 [†]
edL	100	99.6 ± 1.6	98.9 ± 2.1	98.3 ± 2.6	98.0 ± 2.8
fMSS	21.1 ± 1.3	22.5 ± 1.2*	23.0 ± 1.3	22.6 ± 1.8	23.1 ± 1.8
PowI	100	128 ± 8*	146 ± 10 [†]	150 ± 10 [†]	178 ± 15 [†]
LAD					
Q	38.6 ± 8.5	24.3 ± 3.1*	24.2 ± 2.9	23.5 ± 3.1	22.7 ± 3.1 [†]
R	2.2 ± 0.2	3.2 ± 0.2*	3.1 ± 0.2	3.1 ± 0.3	3.3 ± 0.3
edL	100	107.4 ± 1.5*	107.3 ± 1.4	108.1 ± 1.6	108.8 ± 1.5
fMSS	24.5 ± 2.5	12.0 ± 1.2*	9.8 ± 1.3 [†]	8.3 ± 1.2 [†]	7.0 ± 1.6 [†]
PowI	100	59 ± 4*	53 ± 3 [†]	48 ± 7 [†]	43 ± 9
PtO ₂	66 ± 8	22 ± 8*	20 ± 7	19 ± 7	19 ± 8
MVO ₂	2.4 ± 0.4	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	1.7 ± 0.2
MLac	0.64 ± 0.19	-1.74 ± 0.22*	-1.90 ± 0.26	-1.99 ± 0.24	-2.12 ± 0.29

Mean ± SEM ($n = 8$); $2p < 0.05$, *stenosis vs control, [†]Lev vs stenosis.

Q = coronary artery blood flow [$\text{ml} \cdot \text{min}^{-1}$]; R = coronary flow resistance [$\text{mmHg} \cdot \text{ml}^{-1} \cdot \text{min}$]; edL = normalized myocardial enddiastolic segment length [%]; fMSS = fractional myocardial systolic shortening [%edL]; PowI = normalized myocardial power index [%]; PtO₂ = myocardial oxygen pressure [mmHg]; MVO₂ = myocardial oxygen uptake [$\text{ml} \cdot \text{min}^{-1}$]; M_{Lac} = myocardial lactate uptake (+) or release (-) [$\text{mg} \cdot \text{min}^{-1}$].

fMSS_{LCX}: -5%). The other variables showed no significant changes in response to i.v. vehicle.

Levosimendan: Global haemodynamics (Table 1)

Following application of levosimendan a significant increase was observed for heart rate (HR: +22 beats/min), cardiac output (CO: +17%), and dP/dt_{max} (+21%). A decrease occurred in response to levosimendan for central venous pressure (CVP: -2.0 mmHg), mean aortic pressure (AoP: -6 mmHg), left ventricular end-diastolic pressure (LVedP: -3.8 mmHg), and systemic vascular resistance (SVR: -21%). Pulmonary

artery pressure, pulmonary vascular resistance, and dP/dt_{min} were not affected significantly.

Levosimendan: Non-ischaemic LCX area (Table 2, Figs. 2 and 3)

Levosimendan did not significantly affect end-diastolic length and systolic shortening of the normally perfused myocardial segments. The regional myocardial power index, however, did significantly increase following levosimendan (PowI_{LCX}: +78%). LCX vascular resistance declined with increasing levosimendan (R_{LCX}: -24%) and LCX blood flow was slightly increased following the 3rd bolus of levosimendan (Q_{LCX}: +15%).

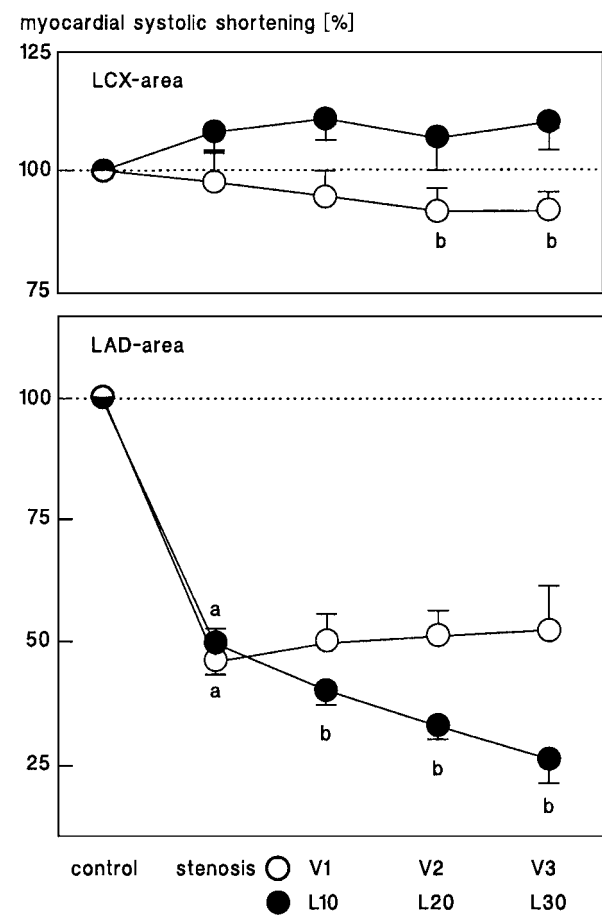


Fig. 2. Myocardial systolic shortening of areas supplied by the left circumflex (LCX) and left descending (LAD) coronary artery following LAD-narrowing by a snare (stenosis) and subsequent intravenous application of levosimendan (L10–L30) and the vehicle of the drug (V1–V3). $p < 0.05$ stenosis vs control (a) and L vs stenosis (b).

Levosimendan: Ischaemic LAD-area (Table 2, Figs. 2 and 3)

Following levosimendan, myocardial end-diastolic length of the ischaemic myocardium did not change. The impaired systolic shortening of the ischaemic area, however, was further reduced dose dependently with increasing levosimendan (fMSS_{LAD}: from 49% to 29% of control). The myocardial power index of the area was also decreased. The LAD blood flow was slightly diminished after the 3rd bolus of levosimendan (Q_{LAD}: –7%). Myocardial oxygen pressure and oxygen uptake did not change with levosimendan. Lactate release from the ischaemic myocardium did increase in 6 out of 8 animals following levosimendan (mean change, however, did not reach the level of statistical significance).

Discussion

Reduction of regional myocardial blood supply by LAD constriction caused an increase in myocardial end-

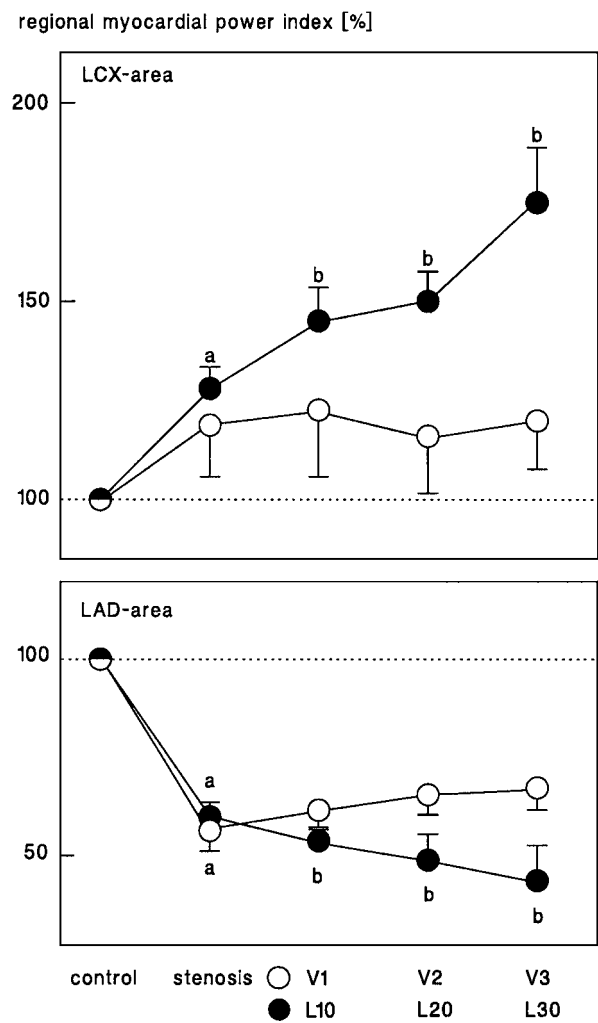


Fig. 3. Myocardial power index of areas supplied by the by the left circumflex (LCX) and left descending (LAD) coronary artery following LAD-narrowing by a snare (stenosis) and subsequent intravenous application of levosimendan (L10–L30) and the vehicle of the drug (V1–V3). $p < 0.05$ stenosis vs control (a) and L vs stenosis (b).

diastolic length and a diminished myocardial systolic shortening and power distal to the stenosis as typically observed following myocardial ischaemia [12–14]. The reduction of myocardial performance during hypoperfusion is usually accompanied by a decrease in myocardial oxygen consumption [15–17]. In the present study, however, a decrease in MVO₂ was not observed in each experiment. This finding may be due to anatomical facts, causing that the sampled coronary venous blood did not drain exclusively from the hypoperfused LAD area but less or more from the LAD area with reduced MVO₂ and from the adjacent non-ischaemic myocardium.

The intravenous application of levosimendan significantly affected haemodynamics and regional

myocardial function as compared to the vehicle of the drug. The observed effects agree with the pharmacodynamic profile of the drug [18]: positive chronotropic and inotropic action, and vasodilatation.

In the present experiments, an increase in contractility following levosimendan is reflected by the increase in dP/dt_{\max} . The end-diastolic length and the systolic shortening of the non-ischaemic myocardium showed no significant changes. The myocardial power index increased, however, showing an improved myocardial performance, which agrees also with the positive inotropic action of the drug.

Concerning vasodilatation following levosimendan, the present data confirm systemic vasodilatation [4,19–21] as indicated by the decrease in systemic vascular resistance, venous [4,22] as suggested by the decrease in central venous pressure, and vasodilatation in the intact coronary circulation [21] as demonstrated by the decrease in the coronary vascular resistance in the LCX area. The coronary vascular resistance of the constricted LAD did not change following levosimendan. This is explained by an exhausted coronary flow reserve distal to a functionally effective stenosis [13].

Pulmonary vascular resistance was not affected by levosimendan in the present experiments. Similarly, the drug showed no significant effect on pulmonary vascular resistance in patients with left ventricular dysfunction [23]. In contrast, a reduction in pulmonary vascular resistance by levosimendan was described in patients with congestive heart failure [24], decompensated heart failure [25], after surgery in low risk patients subjected to elective coronary artery bypass grafting [20,26], and for anaesthetised pigs [27]. The data from the patients are scarcely to compare with the present animal results. The reason for different effects in these studies may be dose related. At highest dosage, there may be a definite contribution of PDE III inhibition by levosimendan because the heart rate could not be increased by the effect on Ca^{2+} sensitivity.

The outstanding result of the present experiments is the effect of levosimendan on the function of myocardium with limited blood supply. This experimental model with a functionally effective coronary artery stenosis was chosen to simulate the situation of acute myocardial hypoperfusion as in patients with *angina pectoris*. In contrast to the functional improvement of intact myocardium, the already impaired performance of the hypoperfused myocardium became further reduced dose dependently by levosimendan and the lactate production showed an increasing trend in this area. Obviously, the imbalanced oxygen demand and supply ratio further worsened. Myocardial oxygen demand probably increased following levosimendan due to the increase in heart rate. Concerning the oxygen supply, the systemic vasodilatation caused a small but significant decrease in aortic pressure and thus in coronary perfusion pressure. The coronary flow reserve distal to the stenosis was exhausted, however. Thus, the reduced perfusion pressure was not to compensate for by

vasodilatation and LAD blood flow decreased. Indeed, this reduction in LAD blood flow was rather small. But at a flow level, where systolic shortening is reduced by 50%, a small decrease in flow further impairs myocardial performance [13].

Levosimendan was supposed to increase myocardial efficiency [4,20], i.e. myocardial performance improves without an increase in oxygen demand, or myocardial power is maintained at a reduced oxygen demand. This feature would be very beneficial in myocardium with limited oxygen supply. In the present study, the decreasing power index and increasing lactate release of the hypoperfused myocardium following levosimendan contradict an improved myocardial efficiency. But these data from ischaemic myocardium distal to a functionally effective fixed coronary stenosis are hardly to compare to the above mentioned studies. These were performed in healthy dogs [4] and in patients after successful coronary artery bypass grafting [20], oxygen consumption was not measured but estimated from the pressure work index [4], and the reduction in afterload following levosimendan, which can be assumed to decrease myocardial oxygen uptake, was not taken into account [20]. In another study, levosimendan did not affect left ventricular efficiency in patients with decompensated congestive heart failure [28]. Levosimendan improved cardiac output and myocardial contractility in a pig model of coronary artery ligation and reperfusion [29]. However, the method differs significantly from our model using LAD stenosis, which makes a comparison of the findings difficult.

Recently, preliminary results from the LIDO study were presented [9]. This clinical trial includes patients with severe heart failure ($EF < 35\%$, $CI < 2.5 \text{ l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, $PCWP > 15 \text{ mmHg}$), who need i.v. treatment with positive inotropic drugs. The study compares the outcome following treatment with a 24 h infusion of either dobutamine or levosimendan. Death or worsening of the heart failure during 30 days following treatment was significantly lower in the levosimendan group than in the dobutamine group (6.8% vs 18.4%). According to these promising data, levosimendan seems superior to dobutamine in the treatment of decompensated heart failure. Levosimendan was recently shown to open ATP sensitive potassium channels (K_{ATP}) [30] and to reduce myocardial infarct size in this way [31].

Whether levosimendan is also superior to catecholamines or pure phosphodiesterase inhibitors to support ischaemic myocardium with limited oxygen supply remains open. From the point of view of performance of ischaemic myocardium, levosimendan is not to be recommended according to the present data.

Acknowledgments

Levosimendan was generously supplied by Orion Pharma, Espoo, Finland. The study was supported by Dr. Helmut Legerlotz-Stiftung, München.

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