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Intracoronary and Intravenous Magnesium Does Not Reduce Myocardial Infarct Size in a Canine Model of Regional Ischaemia and Reperfusion

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Clinical trials show controversial effects of magnesium infusion in patients with acute myocardial infarction. In LIMIT-2, intravenous magnesium lowered mortality, but in the much larger ISIS-4, intravenous magnesium had no effect. Because of these conflicting results, we tested two hypotheses in a dog model of ischaemia and reperfusion.

A) Intracoronary magnesium infusion given in the early reperfusion period has a protective effect against myocardial reperfusion injury.

B) Systemic magnesium-potassium infusion with doses comparable to those used in clinical studies, may reduce myocardial infarct size.

Anaesthetized open chest dogs underwent 1 h of left anterior descending artery occlusion followed by 6 h of reperfusion.

A) Animals received intracoronary magnesium aspartate (Mg i.c., n = 5) or vehicle infusion (Control i.c., n = 5) for the first hour of reperfusion to increase regional plasma concentration by 4 mmol l^{-1}.

B) Animals received intravenous magnesium-potassium-aspartate (Mg-K i.v., n = 6) or vehicle infusion (Control i.v., n = 8) beginning 1 h before occlusion until the end of the 6 h reperfusion period.

Intracoronary magnesium had no influence on infarct size (Mg i.c. 20.6 ± 5.0 % of area at risk, Control i.c. 24.4 ± 8.7 % of area at risk, P = ns) or regional post-ischaemic wallfunction. Application of intravenous magnesium-potassium did not reduce myocardial infarct size (Mg-K i.v. 14.1 ± 14.8 %; Control i.v. 18.1 ± 12.2 % of area at risk; P = ns). The possible beneficial effect of magnesium infusion is probably not due to an early, direct protective effect on ischaemic-reperfused myocardium. *J Clin Basic Cardiol 2002; 5: 23–28.*

Key words: dog, heart, infarct size, ischaemia, reperfusion, magnesium, myocardial infarction

Several randomised clinical trials, eg the Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), have shown beneficial effects of magnesium infusion in patients with acute myocardial infarction [1]. In contrast, the Fourth International Study of Infarct Survival (ISIS-4) failed to show any protective effect of magnesium infusion [2]. There are a number of actions of magnesium on the cardiovascular system that could have influenced these diverging results [3]. Besides its antiarrhythmic [4, 5] and antithrombotic [6, 7] functions, magnesium can protect the ischaemic-reperfused myocardium [8–10]. Reperfusion injury, structural damage following ischaemia and reperfusion, is caused by energy rich metabolites and oxygen reperfusing the energy-depleted myocardium [11, 12]. Magnesium may influence these mechanisms as well as acting as a natural calcium antagonist, preventing ischaemic calcium overload [13]. Experimental studies on both canine and swine models have underlined the importance of magnesium administration prior to the onset of reperfusion [14, 15].

In this study we tested the hypothesis that magnesium can reduce myocardial infarct size in a model of regional ischaemia and reperfusion in the anaesthetized dog after coronary artery occlusion. To examine a direct effect of magnesium on the reperfused myocardium, the animals received intracoronary magnesium for the first hour of reperfusion to increase the regional magnesium plasma concentration by 4 mmol l^{-1} in the coronary arteries, an elevation that did not alter the electrophysiological excitation of the heart [16, 17]. Since a combination of magnesium and potassium has been shown to reduce reoxygenation arrhythmias [4] in a second study, animals received intravenous magnesium potassium aspartate starting before the occlusion and until the end of reperfusion, in a dose comparable to that which could be achieved clinically.

Materials and Methods

Animal preparation

Twenty-four mongrel dogs of either sex, weighing 18 to 34 kg, were anaesthetized with sodium thiamylal, anaesthesia was maintained with enflurane in a mixture of oxygen/nitrous oxide. For further details see [18].

After thoracotomy and pericardiotomy as illustrated in Figure 1, sonographic crystals were implanted into the epicardial and subendocardial myocardium of the anterior wall perfused by the left anterior descending artery (LAD) and the posterior wall perfused by the left circumflex artery (LCX) as a control region. These crystals were used to determine regional wall thickness by sonomicrometry. A suture was placed around the LAD for later occlusion. Left ventricular pressure (LVP) was measured with a catheter tip manometer through the left auricle of the heart. Coronary blood flow of LCX and LAD at the site of occlusion were measured with ultrasonic flow probes. Ischaemic regional myocardial blood flow (RMBF) during the occlusion was measured using coloured microspheres in the group of intravenous treatment. For further details see [19].

After the end of the reperfusion period, hearts were arrested in diastole with Bretschneider's cardioplegic solution via the aorta. The area at risk was perfused with Dextran in sodium chloride via the LAD, the rest of the heart was perfused with 0.2 % Evans blue, staining the non-risk-area

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blue. After excision of the heart, transversal slices of the left ventricle were stained with triphenyltetrazolium chloride (TTC) to identify necrotic tissue by its red colour [20, 21]. Myocardial infarct size was assessed by planimetry.

Drug preparation

A) Intracoronary magnesium

The solutions used for anoxic pre-reperfusion contained 20 mmol l^{-1} HEPES (N-2-hydroxyethylpiperazin-N'-2-ethanesulfonic acid) and either 2 mmol l^{-1} magnesium-aspartate (Mg i.c., n = 5) or 12.5 mmol l^{-1} sodium-chloride (control i.c., n = 5) adjusted to pH 7.4 and equilibrated with 100 % N_2. Normoxic infusion contained 20 mmol l^{-1} magnesium-aspartate or 145 mmol l^{-1} sodium-chloride, each buffered with HEPES and adjusted to pH 7.4.

B) Intravenous magnesium and potassium

The infusion for the intervention group (Mg-K i.v., n = 6) contained 16.6 mmol l^{-1} magnesium-aspartate and 16.6 mmol l^{-1} potassium-aspartate and 0.1 mmol l^{-1} HEPES adjusted to pH 7.35 and sodium chloride 0.9 %. Animals of the placebo group (Control i.v., n= 8) received sodium-chloride 0.9 %.

Experimental protocol

After surgical preparation, sufficient time was allowed for stabilization of the haemodynamic parameters. Baseline values were then measured. The hearts of Group A were paced via the left atrium throughout the experiment.

A) Intracoronary magnesium

The animals underwent 60 min of LAD occlusion with subsequent 360 min of reperfusion. Anoxic intracoronary perfusion of the LAD was administered for the last 5 min of the occlusion with a rate of 10 ml min^{-1}, followed by normoxic intracoronary infusion for the first 60 min of reperfusion. The infusion rate was adapted to LAD-flow to increase regional plasma concentration by approximately 4 mmol l^{-1} (Fig. 1A).

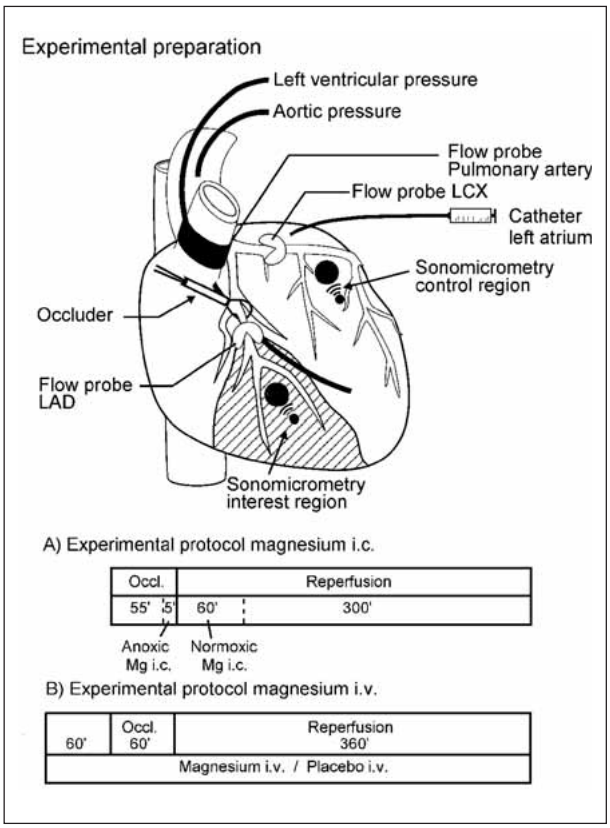

Figure 1. Experimental preparation and protocol of intracoronary magnesium (A) and intravenous magnesium (B) (time in min)

B) Intravenous magnesium and potassium

Sixty minutes after baseline measurements the animals underwent 60 minutes of LAD occlusion followed by 360 min of reperfusion. Either saline or Mg-K aspartate were administered intravenously using a foreleg vein after completing baseline measurements 60 minutes before occlusion until the end of reperfusion. The infusion rate for both groups was 0.1 ml min^{-1} [kg body weight]$^{-1}$, that is 0.1 mmol magnesium potassium aspartate per hour and kg body weight (Fig. 1B). In contrast to the protocol using intracoronary infusion, animals were not paced.

Data analysis and statistics

LVP, its first derivative d*P*/d*t*, anterior and posterior wall thickness, coronary blood flow in the LAD and the LCX were continuously recorded on an ink recorder. The signals were stored on videotapes after pulse-code modulation. The data were digitized with an analogue-to-digital recorder at a sampling rate of 500 Hz and processed on a personal computer. Systolic wall thickening (WTh_{SYS}) as a parameter for regional myocardial wall function was calculated by the following formula:

$$WTh_{SYS} = (WTh_{ES} - WTh_{ED}) / WTh_{ED} \times 100$$

where WTh_{ES} stands for wall thickness at the end of systole and WTh_{ED} for wall thickness at the end of diastole.

All data are expressed as means ± standard deviation. Analysis was carried out by an analysis of variance (ANOVA) followed by a Duncan *post-hoc* test or a *t*-test for independent samples. Differences with a level of significance $P < 0.05$ were considered as statistically significant.

Results

Serum magnesium and potassium

A) Intracoronary magnesium

Under baseline conditions systemic serum magnesium concentration was 0.65 ± 0.05 mmol l^{-1}. During intracoronary infusion systemic serum magnesium increased to 0.99 ± 0.05 mmol l^{-1} at 15 min reperfusion ($P < 0.001$ vs. Control i.c.) with a maximum of 1.19 ± 0.08 mmol l^{-1} at the end of intracoronary infusion ($P < 0.001$) and returned to baseline values by the end of the experiment.

B) Intravenous magnesium and potassium

Infusion as illustrated in Figure 2, induced a significant increase of systemic serum magnesium from 0.71 ± 0.02 mmol l^{-1} at baseline to 1.42 ± 0.29 mmol l^{-1} at the end of reperfusion ($P < 0.01$ vs. baseline and Control i.v.). With the onset of reperfusion serum magnesium was significantly elevated ($P < 0.05$ vs. control and baseline; Mg-K i.v.: 1.29 ± 0.20 mmol l^{-1}; Control i.v.: 0.81 ± 0.24 mmol l^{-1})

Serum potassium was not increased in either the control or the Mg-K-groups.

Global haemodynamics

A) Intracoronary magnesium

Peak systolic left ventricular pressure (LVP_{MAX}), maximal and minimal left ventricular d*P*/d*t* (d*P*/dt_{MAX} and d*P*/dt_{MIN}) were not different within the groups. LVP_{MAX} was stable dur-

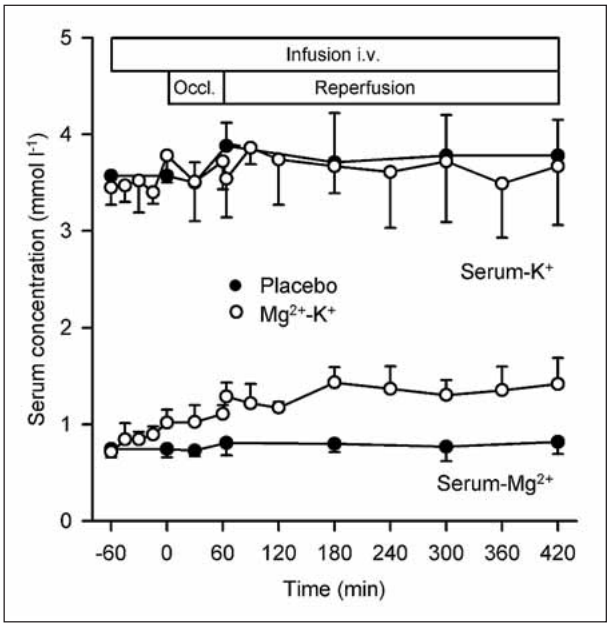

Figure 2. Total serum concentration of magnesium and potassium during intravenous infusion of magnesium potassium aspartate or placebo. Occl. = time period of left anterior descending artery occlusion; Reperfusion = time period of reperfusion of the left anterior descending artery; Infusion i.v. = time period when magnesium potassium aspartate or placebo was infused intravenously; values are means ± SD

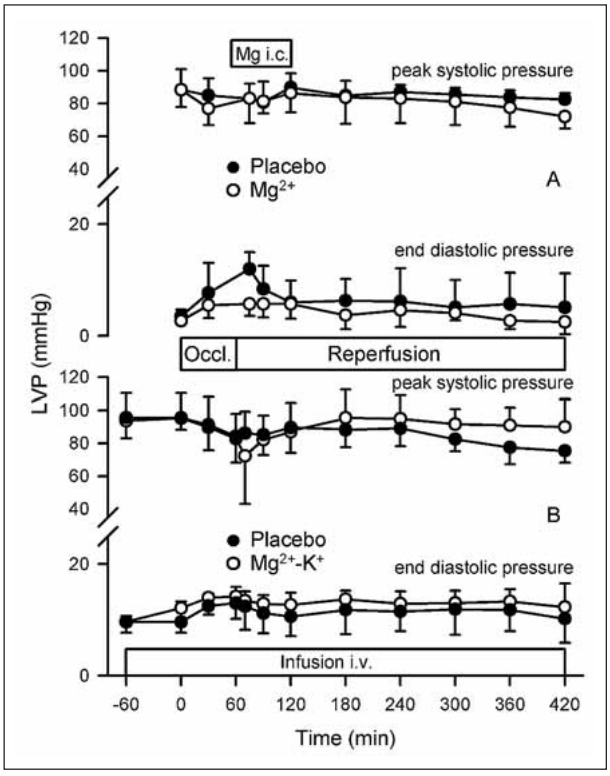

Figure 3. Left ventricular pressure (LVP) during intracoronary magnesium aspartate use (A-upper panel) and intravenous magnesium potassium aspartate use (B-lower panel). Occl. = time period of left anterior descending artery occlusion; Reperfusion = time period of left anterior descending artery reperfusion; Mg i.c. = time period when magnesium aspartate or vehicle was infused into the left anterior descending artery; Infusion i.v. = time period when magnesium potassium aspartate or vehicle was infused intravenously; values are means ± SD

ing the experiment (Fig. 3A), in both groups dP/dt_{MIN} was decreased with onset of the occlusion and remained depressed during reperfusion (Tab. 1).

B) Intravenous magnesium and potassium

Treatment with Mg-K decreased heart rate at the beginning of occlusion ($P < 0.05$ vs. baseline). While animals of the control group showed an increase in HR during the experiment, Mg-K induced an increasing bradycardia from 114.1 ± 7.1 min^{-1} to 100.2 ± 16.7 min^{-1} (Fig. 4). LVP_{MAX} was similar in both groups (Fig. 3B).

There was no difference in the maximal dP/dt representing left ventricular inotropy (Tab. 1).

Regional haemodynamics

A) Intracoronary magnesium

Systolic wall thickening as a parameter of regional function is shown in Figure 5A. WTh_{SYS} of the test region was similar in both groups, it decreased with LAD occlusion to negative values, the depression remaining even during the reperfusion period. Ischaemic myocardium lost its ability to contract, so the systolic myocardial wall thickness is not greater than diastolic values. The myocardial wall was even thinned by surrounding non-ischaemic regions so that the ratio shows negative values.

Regional wall function of the control region was similar in both placebo and magnesium groups during the experiment.

B) Intravenous magnesium and potassium

Depression of WTh_{SYS} of the ischaemic region occurred in both groups commencing with the start of LAD occlusion, similar to the i.c. study (Fig. 5B).

Regional wall function of the control region was better in the Mg-K group ($P < 0.001$). Improvement of WTh_{SYS} was not only limited to the ischaemic period, the Control i.v.-group also showed a mild improvement of WTh_{SYS}.

Infarct size

A) Intracoronary magnesium

Application of magnesium did not reduce the infarct size as illustrated in Figure 6 ($P = 0.41$; Mg i.c. 20.6 ± 5.0 % of area

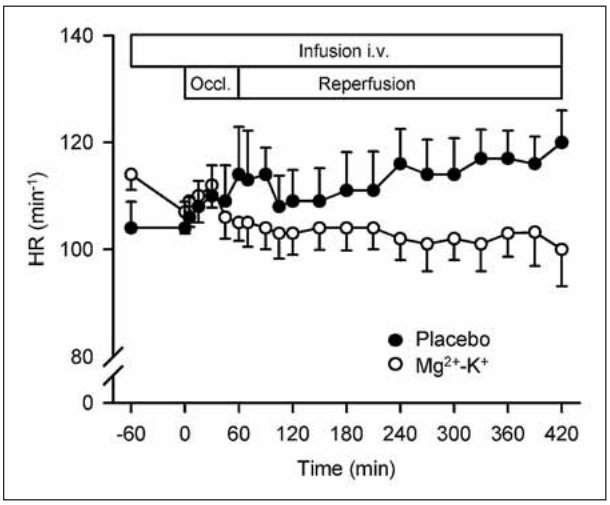

Figure 4. Heart rate during administration of intravenous magnesium potassium aspartate in ischaemia-reperfusion. HR = heart rate; Occl. = time period of left anterior descending artery occlusion; Reperfusion = time period of reperfusion of the left anterior descending artery; Infusion i.v., time period when magnesium potassium aspartate or vehicle was infused intravenously; values are means ± SD; Mg^{2+}-K^+ vs Control; $P < 0.001$

at risk; Control i.c. 24.4 ± 8.7 %). Area at risk was equal (Mg i.c. 28.0 ± 7.4 % of the left ventricle; Control i.c. 29.6 ± 8.6 % of the left ventricle).

B) Intravenous magnesium and potassium
Myocardial infarct size was not reduced by Mg-K as shown in Figure 6 (P = 0.61). The mean infarct size was 18.1 ± 14.7 % of area at risk for the control group, the mean infarct size in the Mg-K-group was 14.1 ± 12.2 % of the area at risk. Size of the area at risk was not different (Control i.v.: 35.6 ± 8.2 % of the left ventricle; Mg-K i.v.: 36.7 ± 11.3 % of the left ventricle).

Regional myocardial blood flow
Ischaemic collateral blood flow did not differ in the animals of the intravenous treatment-study. No differences in epicardial, endocardial or transmural areas were observed.

Discussion

The main result of the intracoronary magnesium study is that there is no protective effect of magnesium against myocardial reperfusion injury; myocardial infarct size and post-ischaemic wall function were not improved by magnesium infusion. Magnesium has been shown to protect against reperfusion injury, eg prevention of mitochondrial calcium overload [9] or preservation of ATP [8], in isolated rodent hearts [22]. However, the comparison to *in vivo*-studies is difficult, because of the differences in the concentrations used. Concentrations of *in vitro*-experiments cannot be achieved with either intravenous or intracoronary administration in *in vivo*-studies due to the systemic toxicity of high magnesium concentrations [23]. Because of this we chose magnesium concentrations comparable to LIMIT-2 or ISIS-4 to avoid the supratherapeutic effects of magnesium.

After failing to see a protective effect with an elevation of regional serum magnesium by 4 mmol l^{-1} in the intracoronary treatment, we examined in a second study the effect of systemic magnesium-potassium administered in a dose comparable to clinical trials. This study of intravenous magnesium-potassium-administration also failed to show an infarct-size reduction. The regional wall function of post-ischaemic myocardium was also not improved.

After intravenous infusion, serum magnesium was nearly doubled, while potassium was not different to baseline value. Increased renal excretion of potassium was not observed. A possible explanation for this difference is a rapid cellular uptake of potassium but not for magnesium.

In vitro-studies have shown a protective effect of magnesium, but concentrations used are difficult to reproduce in a physiological or clinical setting [4, 10, 24]. When magnesium is given in supratherapeutic doses, negative inotropy occurs. The protective effect of negative inotropic substances in myocardial infarction is well known eg β-blockers, Ca^{2+}-receptor antagonists or volatile narcotics [25–27]. In this study we used concentrations of magnesium that showed no changes in maximal d*P*/d*t*, a marker for negative inotropy. The improved myocardial wall function of the posterior wall, that is seen in the i.v. treatment group, is due to a Frank-Starling-mechanism. Bradycardia prolonged diastolic filling time and elevated LVP_{ED}, so end-diastolic wall-thickness becomes thinner, leading to relative improvement of WTh_{SYS}. In the Mg i.c. experiments, wall thickness or WTh_{SYS} did not change, because the hearts were paced, thus eliminating frequency-related effects.

The decrease in myocardial wall function of the test region with onset of occlusion is due to loss of myocytes and contractility reserves, that is followed by myocardial stunning in the reperfusion period [28]. Magnesium did not change these pathophysiologic phenomena, wall function remained depressed, although magnesium has been shown to improve stunned myocardium [29]. The potency of bradycardic agents to reduce myocardial infarct size [30] is well established and the protection is not dependent on the negative inotropic effects [31]. A trend towards smaller infarct size was seen but was not significant. A power analysis was done before the study, the number of dogs was sufficient to detect a reduction in infarct size compared with prior studies of our working group investigating reperfusion injury [18].

The findings of this study that there is no change in infarct size after either intracoronary or intravenous magnesium infusion are in contrast to those of Christensen et al. [14], Herzog et al. [15; reviewed in 32] and the recent experiments of Ravn et al. [33].

In contrast to our study, in those three studies the levels of magnesium reached on infusion were not measured. We measured the concentra-

Table 1. Global haemodynamics

A) Intracoronary magnesium

	LV d*P*/dt_{MAX} (mmHg s^{-1})		LV d*P*/dt_{MIN} (mmHg s^{-1})	
Intervention	**Control i.c.**	**Mg-K i.c.**	**Control i.c.**	**Mg-K i.c.**
Baseline	1566 ± 121	1583 ± 167	–1993 ± 531	–1800 ± 384
Occlusion				
30 min	1363 ± 229	1380 ± 165	–1555 ± 452*	–1435 ± 247*
Reperfusion				
15 min	1202 ± 246	1413 ± 134	–1041 ± 134*	–1290 ± 384*
30 min	1338 ± 228	1419 ± 220	–1111 ± 261*	–1562 ± 363*
1 h	1472 ± 190	1577 ± 234	–1382 ± 240*	–1900 ± 476*
2 h	1547 ± 196	1530 ± 211	–1293 ± 206*	–1642 ± 533*
3 h	1492 ± 182	1520 ± 226	–1409 ± 201*	–1577 ± 530*
4 h	1507 ± 209	1451 ± 164	–1402 ± 200*	–1562 ± 450*
5 h	1454 ± 222	1334 ± 119	–1351 ± 205*	–1452 ± 443*
6 h	1486 ± 253	1262 ± 51	–1364 ± 193*	–1304 ± 341*

B) Intravenous magnesium and potassium

	LV d*P*/dt_{MAX} (mmHg s^{-1})		LV d*P*/dt_{MIN} (mmHg s^{-1})	
Intervention	**Control i.v.**	**Mg-K i.v.**	**Control i.v.**	**Mg-K i.v.**
Baseline	1582 ± 295	1517 ± 249	–1915 ± 547	–1854 ± 344
Mg^{2+}-K^{+}		1552 ± 254		–1884 ± 268
Occlusion				
30 min	1525 ± 408	1393 ± 285	–1607 ± 561	–1445 ± 336
60 min	1447 ± 392	1298 ± 292	–1447 ± 481	–1290 ± 375
Reperfusion				
15 min	1332 ± 303	1371 ± 225	–1461 ± 558	–1165 ± 418
30 min	1420 ± 356	1410 ± 231	–1544 ± 450	–1294 ± 314
1 h	1510 ± 336	1524 ± 274	–1660 ± 532	–1430 ± 288
2 h	1592 ± 392	1489 ± 238	–1567 ± 522	–1444 ± 297
3 h	1489 ± 337	1455 ± 249	–1518 ± 394	–1333 ± 314
4 h	1422 ± 348	1383 ± 171	–1403 ± 297	–1307 ± 243
5 h	1391 ± 298	1425 ± 195	–1251 ± 329	–1339 ± 237
6 h	1261 ± 214	1321 ± 201	–1250 ± 223	–1250 ± 388
	P = ns		P < 0.01	

Values are means ± SD; LV d*P*/dt_{MAX} = maximum of first derivative of left ventricular pressure; LV d*P*/dt_{MIN} = minimum of first derivative of left ventricular pressure, * P < 0.05 vs baseline

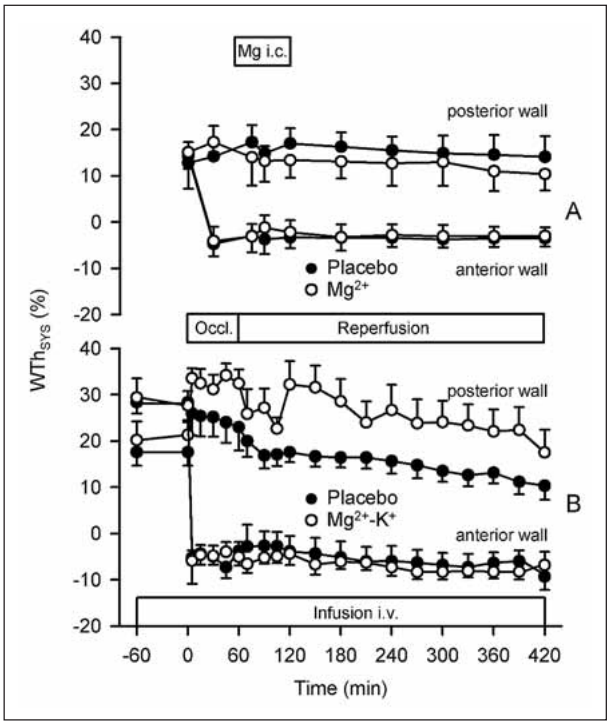

Figure 5A: Left ventricular pressure (LVP) during intravenous infusion of magnesium potassium aspartate or placebo.
Figure 5B: Regional wall function in the anterior (ischaemic) and posterior (non-ischaemic) wall during intracoronary infusion of magnesium aspartate or vehicle (A-upper panel) and intravenous infusion of magnesium potassium aspartate or vehicle (B-lower panel). WTh_{SYS} = systolic wall thickening; Occl. = time period of left anterior descending coronary artery occlusion; Reperfusion = time period of left anterior descending artery reperfusion; Mg i.c. = time period when magnesium aspartate or vehicle was infused into the left anterior descending artery; Infusion i.v. = time period when magnesium potassium aspartate or vehicle was infused intravenously; values are means ± SD

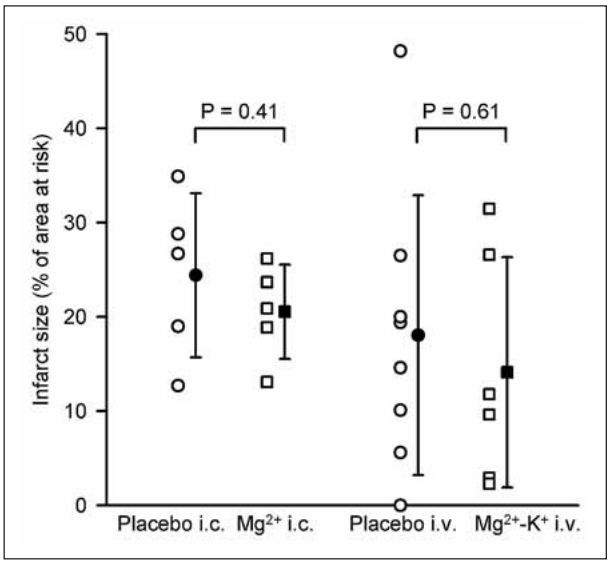

Figure 6. Infarct size as percentage of area at risk after intracoronary magnesium aspartate or placebo and intravenous magnesium potassium aspartate or placebo; values are single values and means ± SD (filled symbols)

tion of total magnesium, but the concentration of ionised magnesium, which is responsible for the biological effects was not measured. Aspartate could bind Mg^{2+} and thus reduce the ionised concentration, but recent measurements of such binding with Mg^{2+}-macroelectrodes showed that aspartate did not significantly bind Mg^{2+} and reduce the ionised Mg^{2+} concentration [34]. Different protocols, with or without initial bolus of magnesium were also used which could also have influenced the magnesium concentrations. The lack of the possibility to compare serum concentrations of magnesium during occlusion and at the onset of reperfusion makes it difficult to explain the different results concerning infarct size reduction. It is thus essential in future studies, to measure both total and ionised magnesium concentrations to allow comparison amongst different studies.

In conclusion, our results on anaesthetized animals do not support a beneficial effect of magnesium infusion for patients with acute myocardial infarction. Indeed, magnesium infusion could even be detrimental, as the Second National Registry of Myocardial Infarction [35] concluded that there is tendency to an increased mortality in those patients who received an infusion of magnesium.

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This study was approved by the Bioethics Committee of the District of Düsseldorf, Germany.

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