Cardiovascular Topics

Effect of magnesium on myocardial ischaemia and reperfusion injury

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Summary

This study examined the effect of intravenous magnesium on the reperfusion injury of the porcine myocardium. Animals received general anaesthesia and the left anterior descending coronary artery was occluded for 15 minutes. Thereafter, reperfusion was allowed for 60 minutes. Regional ventricular function was measured with microsonometers. Animals were randomly assigned to a control (N = 6) or a magnesium group (N = 6). The latter received 30 mg/kg magnesium immediately before the release of the occlusion on the left anterior descending (LAD) artery.

Results indicate that magnesium administration is associated with fewer ventricular arrhythmias and a rapid recovery (within 5 minutes) of myocardium systolic function once reperfusion was initiated. In the control group myocardial stunning was prolonged and more reperfusion arrhythmias occurred. However, in the group that received magnesium there was more diastolic dysfunction during reperfusion.

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Myocardial reperfusion injury consists of arrhythmias, accelerated cell death and prolonged reversible post-ischaemic dysfunction (stunning).[1] A number of possible explanations have been proposed, but the generation of free oxygen radicals, leading to intracellular calcium overload and prolonged dysfunction, is currently a popular explanation for reperfusion injury.[2-5] This conclusion is further confirmed by data which demonstrate that the modulation of intracellular calcium overload early in the reperfusion period decreases myocardial stunning.[6-8]

Magnesium has been termed nature's physiological calcium blocker.[9] Excess magnesium blocks and a deficiency of magnesium accentuates the actions of calcium. This has led to various studies that have examined the effect of magnesium on experimental myocardial ischaemia and infarction,[10-13] as well as to clinical trials that have examined the hypothesis that magnesium may be beneficial to the patient who has had a myocardial infarction.[14-17]

Two experimental studies examined the effects of magnesium on regional myocardial performance during stunning.[18,19] They demonstrated that magnesium supplementation improved, and magnesium depletion aggravated, stunning. However, both studies were performed under isoflurane anaesthesia, while previous studies suggest that isoflurane improves myocardial stunning.[20,21] In addition, these studies did not address the effect of magnesium on reperfusion arrhythmias.

The aim of this study, therefore, was to evaluate the effect of magnesium administered immediately before the initiation of reperfusion on myocardial reperfusion injury, with emphasis on the incidence of reperfusion arrhythmias and stunning.

Methods

This study was conducted with the permission of the Ethics Committee of the University of Stellenbosch Medical School and animals were cared for in accordance with institutional and international guidelines.

Twelve pigs were premedicated with intramuscular ketamine (5 mg/kg). An intravenous infusion of 0.9% NaCl was started in an ear vein and anaesthesia was induced with pentobarbital (8 mg/kg; Entha-naze, Centaur, SA) and lorazepam (1 mg) administered intravenously. With loss of the eyelid reflex, a tracheotomy was performed, the trachea was intubated, and the animals were ventilated with 50% oxygen and nitrogen. The tidal volume was set at 15 ml/kg and the rate adjusted to maintain the end-expired PCO_2 at 35 mmHg. Anaesthesia was maintained with a constant infusion of pentobarbital (3 mg/kg/h) and fentanyl (Tanyl; Intramed, SA), given initially as a bolus of 20 μg/kg and then followed by a constant infusion of 10 μg/kg/h. Muscle relaxation was achieved with vecuronium (Norcuron; Omnimed, SA), initially administered as a bolus of 0.2 mg/kg followed by a constant infusion of 0.3 mg/kg/h.

Temperature of the animals was maintained between 36.5 and 37.5°C using an under-table heating device, and 0.9% NaCl (13 ml/kg/h) was used as maintenance intravenous fluid.

A neck dissection was performed and a stiff cannula inserted into the proximal aorta via the internal carotid artery. This was connected to a transducer (Medex; Medex Med Inc., UK) and was used to measure aortic systolic, diastolic and mean arterial (MAP) pressures continuously. The latter was obtained from the area under the aortic pressure recording. A pulmonary artery catheter (7F; Arrow, USA) was inserted for the determination of cardiac output (CO) by thermodilution (Edwards; Baxter, USA). This was calculated after injection of 5 ml 5% dextrose over approximately 4 seconds into the proximal port. The average of three values was used for subsequent calculations.

One femoral artery was exposed and a Fogarty occlusion catheter (Fogarty; Baxter, USA) was inserted with the balloon lying above the diaphragm but distal to the left subclavian artery. By inflating the balloon, left ventricular (LV) afterload was raised to allow for the recording of afterloaded beats.

A sternotomy and pericardectomy were performed. A 1 cm length of the left anterior descending (LAD) coronary artery distal to the first diagonal branch was mobilised from the underlying muscle and a silk loop was placed around the artery. This was used to occlude the LAD during the protocol.

A stiff 16-gauge cannula was inserted into the LV cavity through an apical stab incision and connected to a transducer (Medex, UK) for continuous recording of LV systolic, diastolic and end-systolic pressures (Pes). Pes was taken at the time the aortic valve closed (as judged from the dicrotic notch on the aortic pressure recording).

Two pairs of microsonometers were inserted into the LV subendocardium, one pair in the region supplied by the LAD artery (distal to the proposed occlusion) and the second in the region supplied by the circumflex coronary artery (LX), which was used as control during the interventions. Signals were transduced (Schuessler and Ass., USA) and maximum segment length (Lmax) at the end of diastole, as well as minimum segment length at the end of systole (Lmin), were recorded. The difference between Lmax and Lmin reflected regional segmental shortening (dL). Shortening that occurred after the aortic valve closure was termed post-systolic shortening (PSS), and was expressed as a percentage of the total regional shortening (PSS%). This was an indication of early (isovolaemic) diastolic dysfunction.

LV pressure and regional length signals were combined to give beat-by-beat pressure-length loops. By raising the afterload with the aortic balloon, various pressure-length loops were recorded. The computer recognised the end-systolic pressure-length points of the various loops and performed a linear regression on these points. The slope of this was termed the end-systolic pressure-length relationship or end-systolic elastance (Ees), and was used as an index of regional myocardial contractility.[22,23] The intercept of this regression on the length axis (x-axis) is the extrapolated regional segment length when the pressure is zero. This is the unstressed LV volume (Lo).

The product of the Pes and dL, i.e. the area under the pressure-length loop (excluding the post-systolic shortening), is an index of regional stroke work (RSW).

Before the occlusion of the LAD (see below), 1 mg/kg heparin (Heparin; Intramed, SA) was given intravenously to prevent clot formation in the LAD artery during the period of occlusion.

All the transduced signals were digitised at a sampling rate of 100 Hz by computer, running a custom-made programme (ALAB, written by Ralph Pinna, Paul Baily and Johan Coetzee, SED and Department of Anaesthesiology, University of Stellenbosch). Data were recorded for 30 seconds at zero airway pressure and later redisplayed to evaluate the quality of the measurements.

Statistical analyses included analysis of variance (ANOVA) and the multiple-range test to define homogeneous groups. Proportions were analysed with the chi-squared test, and regression utilised the method of least squares. A probability of $P = 0.05$ was accepted as indicative of a significant difference between values.

Protocol

After completion of surgery, a 20-minute stabilisation period was allowed. Controlled measurements were made (CONTROLS), and thereafter the LAD artery was totally occluded for 15 minutes. Twelve minutes into the occlusion, data were recorded (ISCHAEMIA), whereafter the occlusion was released at 15 minutes. At 5 minutes (REPERFUSION + 5), 30 minutes (REPERFUSION + 30) and 60 minutes (REPERFUSION + 60), data were again recorded.

Animals were randomly assigned to two groups. One group received no treatment before reperfusion (control group), and the other group received 30 mg/kg magnesium sulphate intravenously 2 minutes before reperfusion of the LAD artery (magnesium group).

TABLE I. GENERAL HAEMODYNAMICS (MEAN ± SD)

	HR (beats/min)	*MAP (mmHg)*	*LVEDP (mmHg)*	*CO (l/min)*	*SV (ml)*	*SW (g/m)*	*+ dp/dt (mmHg/sec)*	*–dp/dt (mmHg/sec)*	*Pes (mmHg)*
Control ($N = 6$)									
Control	117.33 ± 9.12	74.00 ± 12.49	4.30 ± 2.39	3.46 ± 0.68	29.67 ± 6.17	29.01 ± 8.59	1 583.50 ± 251.56	–1 430.33 ± 203.44	58.83 ± 9.86
Ischaemia	110.33 ±7.34	74.00 ±12.71	11.98* ±4.51*	3.28 ±0.42	29.76 ±3.34	25.60 ±6.20	1 549.00 ±311.80	–1 450.83 ±306.80	65.88 ±13.63
Reperfusion + 5 min	114.17 ± 8.86	72.33 ± 14.36	8.80 ± 1.54	4.00 ± 0.31	35.18 ± 2.77	30.65 ± 5.80	1 386.37 ± 175.06	–1 390.00 ± 317.04	68.17 ± 10.48
Reperfusion + 30 min	109.67 ±7.87	86.83 ± 7.06	7.47* ± 2.88	3.18 ± 0.47	29.06 ± 4.64	31.63 ± 3.04	1 615.33 ± 221.98	–1 634.50 ± 326.63	76.33 ± 13.21
Reperfusion + 60 min	110.67 ± 15.87	85.00 ± 13.10	6.72 ± 1.84	3.42 ± 0.74	31.35 ± 7.74	33.25 ± 6.71	1 770.17 ± 441.03	1 615.83 ± 220.51	64.38 ± 10.88
Magnesium ($N = 6$)									
Control	102.00 ± 22.15	71.83 ± 13.64	5.62 ± 1.45	3.45 ± 1.02	34.86 ± 10.01	32.89 ±14.40	2 106.83 ±567.18	–1 471.33 ± 417.24	63.78 ± 25.28
Ischaemia	114.50 ± 8.90	70.33 ± 16.52	10.03* ± 4.79	3.38 ±0.74	29.74 ± 7.40	25.67 ± 11.71	1 753.67 ± 321.25	–1 134.67 ± 618.50	65.50 ± 6.24
Reperfusion + 5 min	103.00 ± 19.40	78.33 ± 22.13	11.15* ±2.17	3.20 ± 1.11	32.58 ±13.84	29.94 ± 15.91	1 734.00 ± 429.01	–1 389.67 ± 470.50	65.40 ±23.01
Reperfusion + 30 min	107.83 ± 9.37	81.33 ± 14.49	9.71* ± 3.09	3.42 ± 0.53	31.66 ± 3.33	31.74 ± 8.90	2 002.67 ± 503.61	–1 341.17 ± 371.01	72.83 ±18.82
Reperfusion + 60 min	108.00 ± 22.60	93.60 ± 17.81	10.82* ± 4.56	3.44 ± 0.50	33.23 ± 7.70	36.45 ± 8.20	2 048.50 ± 506.75	–1 696.50 ± 545.41	76.98 ± 11.58

HR = heart rate; MAP = mean arterial pressure; LVEDP = LV end-diastolic pressure; CO = cardiac output; SV = stroke volume; SW = stroke work; dp/at = rate of isovolaemic pressure increase; –dp/dt = rate of pressure decrease during isovolaemic relaxation; Pes = LV end-systolic pressure.
Compares designated value to control:
*$P < 0.01$.

Ventricular extrasystolic beats that were multifocal or that occurred more than three times in any 30-second period, as well as ventricular tachycardia (associated with an acceptable perfusion pressure), were treated with lignocaine 1 mg/kg intravenously. This was repeated if necessary. If ventricular fibrillation occurred or the ventricular tachycardia did not respond to lignocaine, direct myocardial defibrillation was performed using 5, 5, 10, 10, 15 joules (J) in sequence. The doses of lignocaine and the total joules were recorded.

Results

Global myocardial function (Table I)

Global myocardial function remained stable throughout the experiments in both groups. The only variable that did change was the left ventricular end-diastolic pressure (LVEDP), which increased significantly in both groups during the phase of acute LAD occlusion (ISCHAEMIA). LVEDP remained elevated up to 30 minutes in the control and 60 minutes in the magnesium groups.

Regional myocardial function (Table II)

No changes occurred in the region supplied by the circumflex coronary artery.

Occlusion of the LAD artery caused immediate and severe regional dysfunction. Systolic shortening in both experimental groups decreased significantly. The only regional shortening that did occur was in diastole (PSS). This inappropriate shortening was also reflected in the significant decrease in regional stroke work in both groups, which occurred during ischaemia. Extrapolated regional length at the time LV pressure was zero (Lo) increased significantly in the control animals, but the apparent numerical increase failed to reach statistical significance in the magnesium group.

During **reperfusion** regional systolic shortening in the magnesium group recovered quickly so that at 5 minutes' reperfusion dL was no different from its own control value. In the control group, however, regional shortening recovered more slowly and only at 30 minutes' reperfusion was the value for dL not significantly different from its control. The post-systolic shortening in the control group returned to control values at 5 minutes' reperfusion as opposed to the magnesium group where PSS only returned to normal values at 30 minutes' reperfusion.

In both groups the RSW had improved at 5 minutes' reperfusion, which was no different from control at that time.

Reperfusion arrhythmia (Table III)

The control group required significantly more lignocaine as well as more defibrillation than the magnesium group.

Discussion

Results from this study demonstrate that: (*i*) magnesium given before initiation of reperfusion is associated with

TABLE II. REGIONAL MYOCARDIAL FUNCTION (MEAN ± SD)

	LAD						LX						
	Lmax (mm)	*dL (mm)*	*Lo (mm)*	*Ees (mmHg/mm)*	*PSS (%)*	*RSW (mmHg/mm)*	*max (mm)*	*dL (mm)*	*dL% (%)*	*Lo (mm)*	*Ees (mmHg/mm)*	*PSS (%)*	*RSW (mmHg/mm)*
Control ($N = 6$)													
Control	5.94 ± 0.89	1.00 ± 0.34	3.51 ± 0.93	150.30 ± 160.30	0	57.72 ± 20.31	5.44 ± 0.79	0.38 ± 0.20	6.81 ± 2.84	4.18 ± 1.59	424.30 ± 400.80	0	21.66 ± 9.02
Ischaemia	6.59 ± 0.68	0.08* ± 0.12	5.14* ± 1.32	190.33 ± 162.49	95.32‡ ± 25.60	5.85‡ ± 9.27	5.62 ± 0.70	0.38 ± 0.19	6.64 ± 2.57	5.25 ± 0.84	283.13 ±178.72	1.59 ± 3.55	25.97 ± 14.87
Reperfusion + 5 min	6.56 ± 0.86	0.54* ±0.10	5.10* ± 0.45	111.83 ± 54.99	17.83 ± 16.23	37.52 ± 10.40	5.47 ± 0.64	0.30 ± 0.10	5.49 ± 1.35	4.61 ±0.61	300.67 ±186.79	0	21.26 ± 9.69
Reperfusion + 30 min	6.70 ± 0.77	0.76 ± 0.25	3.72 ± 0.56	76.17 ±57.16	13.40 ± 13.31	57.65 ± 22.74	5.63 ± 0.63	0.35 ± 0.10	6.14 ± 1.46	4.85 ± 0.54	287.17 ± 126.83	0	27.75 ± 11.75
Reperfusion + 60 min	6.58 ± 0.82	0.80 ± 0.25	4.02* ± 0.68	67.17 ± 21.69	6.90 ± 8.90	50.57 ± 14.52	5.60 ± 0.65	0.36 ± 0.12	6.43 ± 1.87	4.29 ± 1.30	265.33 ± 151.53	0	23.18 ±8.38
Magnesium ($N = 6$)													
Control	5.88 ± 0.49	0.47 ± 0.31	4.13 ± 1.98	461.17 ± 503.48	0	27.09 ± 18.06	5.57 ± 1.33	0.43 ± 0.14	8.03 ± 2.84	4.83 ± 1.36	325.00 ± 86.55	0	24.43 ± 4.57
Ischaemia	6.21 ± 0.51	0.10* ± 0.10	5.61 ± 0.51	253.33 ±173.04	68.90† ± 4.78	8.69* ± 5.78	5.72 ± 1.44	0.32 ± 0.18	5.24 ± 1.88	4.99 ± 1.14	281.50 ± 146.17	0	20.12 ± 10.23
Reperfusion + 5min	6.10 ± 0.45	0.45 ± 0.32	4.89 ± 0.55	153.67 ± 59.84	30.88† ±30.29	27.77 ± 18.56	5.33 ± 0.72	0.34 ± 0.14	6.30 ± 2.13	4.72 ± 0.84	339.33 ± 226.18	0	23.13 ± 11.62
Reperfusion + 30 min	5.92 ±0.72	0.56 ±0.25	4.26 ±0.76	101.67 ±47.60	3.29 ±5.09	40.79 ±19.73	5.31 ±0.64	0.41 ±0.16	7.68 ±2.74	3.51 ±1.39	277.50 ±169.42	0	30.17 ±15.45
Reperfusion + 60 min	5.97 ± 0.73	0.65 ± 0.34	4.43 ± 1.29	94.67 ± 61.78	3.56 ± 7.37	51.55 ± 29.79	5.30 ± 0.58	0.40 ±0.14	7.53 ± 2.49	4.54 ± 0.67	282.00 ± 271.59	0	30.28 ± 10.65

Lmax = maximum regional length; dL = regional systolic shortening; dL% = dl/max × 100; Lo = LV regional length when LV pressure = zero; Ees = end-systolic pressure - volume relation, PSS = post-systolic shortening; RSW = regional stroke work; LAD and LX = areas supplied by LAD and circumflex coronary arteries.
Compares designated value to own control:
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.

fewer ventricular arrhythmias; (*ii*) systolic function (stunning) recovered more rapidly during reperfusion in animals that received magnesium; and (*iii*) recovery of diastolic function during reperfusion occurred more slowly in the presence of additional magnesium.

Magnesium has been termed 'nature's physiological calcium blocker'.[9] It probably blocks the slow inward current of calcium and stabilises the electrical activity of the sinus node and atrial muscle,[24-26] while intracellular magnesium inhibits the release of calcium from the sarcoplasmic reticulum (SR) during calcium-induced calcium release.[27] Reports suggest that magnesium drives the calcium into the SR by stimulation of the Ca-ATPase enzyme activity,[28] and in addition also competes with calcium at certain binding sites on troponin-C and myosin, thereby decreasing the ability of calcium to increase myocardial tension.[29] It is therefore not unexpected that studies have shown that magnesium decreases myocardial contractility and inhibits certain arrhythmias.[30-35]

Large clinical studies were conducted to evaluate the effect of magnesium administered to patients who had already suffered a myocardial infarction.[14,15,17] The conclusion of the LIMIT-2[14] and ISIS-4[17] studies were, however, contradictory inasmuch as the LIMIT-2 trial showed some benefit while the ISIS-4 trial failed to confirm beneficial effects from magnesium administration. A randomised but smaller study also showed beneficial effects when magnesium was given to patients who had suffered a myocardial infarction.[36] Animal studies of infarct size showed less extensive infarction if magnesium was administered during myocardial ischaemia and the reperfusion period.[11-13]

The timing of the magnesium administration seems to be important, as was demonstrated by Hertzog *et al.*[18] In their animal study the late administration of magnesium (1 hour after reperfusion was initiated) did not limit reperfusion arrthythmias or infarct size. This was in contrast to the beneficial effect obtained from administration of magnesium immediately at the onset of reperfusion.[12] Data suggest that oxygen radical formation peaks at approximately 3 minutes and intracellular calcium overload is maximal at approximately 5 minutes.[4,37] Whatever antagonist is considered will therefore have to be administered during this critical early period of reperfusion or be present when reperfusion is initiated.

This study did not set out to evaluate the effects of magnesium on infarction, but rather to evaluate the effects of magnesium as a mechanism to modulate the reperfusion injury. Previous studies have addressed this issue but were performed under isoflurane anaesthesia.[18,19] Inhalation anaesthetics such as isoflurane have their own protective effects during reperfusion and could therefore have played a role in the results already published.[20,21]

Results from this study can be viewed as support for the theory and previously published results that suggest a protective effect of magnesium during reperfusion.[20,21] The administration of magnesium resulted in less ventricular arrhythmias and reduced the requirements for lignocaine and defibrillation. This beneficial effect of magnesium is probably related to its calcium-blocking effect. Partially depolarised myocardial cells (which do not usually initiate action potentials), can initiate action potentials that can then

TABLE III. ANIMAL WEIGHT, MAGNESIUM BLOOD CONCENTRATION, LIGNOCAINE AND DEFIBRILLATION REQUIREMENTS (MEAN ± SD)

	Control (N = 6)	*Magnesium (N = 6)*
Weight (kg)	27.4 ± 2.65	23.93 1.91
Magnesium (mmol/l)	0.76 ± 0.11	Before mg^{2+} 0.79 ± 0.05 After mg^{2+} 1.67‡ ± 0.15
Lignocaine (mg)	41.3† ± 10.3	13.4 ± 5.9
Joules	41.3* ± 10.3	23.8 ± 8.1

Compare control with magnesium: *$P < 0.05$. †$P < 0.001$.
‡Compare before with after mg^{2+}: $P < 0.0001$.

be blocked by calcium channel blockers or low extracellular calcium. Early afterdepolarisation is also induced by partially depolarised cells and this effect is enhanced by calcium overload of cells. Both early afterdepolarisation and delayed afterpolarisation can be suppressed by low extracellular calcium concentration or calcium channel blockers. Furthermore, calcium channel blockers decrease the tendency towards ventricular fibrillation in ischaemic hearts.[24] Data from rat experiments demonstrated fewer reperfusion arrhythmias in the presence of high magnesium and more conduction pathology in the presence of low magnesium.[38] Iseri[32] discussed the beneficial effects of magnesium on ventricular tachyarrhythmias and concluded that magnesium is a viable option for the management of ventricular tachycardia and fibrillation. Prophylactic magnesium administration to patients undergoing cardiac surgery seems to reduce the incidence and severity of atrial fibrillation, but does not affect the incidence of ventricular arrhythmias.[30] These findings are especially significant considering the low magnesium blood levels reported after cardiac surgery.[39-41]

Results from our study also show that magnesium was associated with less myocardial stunning, which supports the findings of Atar *et al.*[19] and Hertzog *et al.*[18] The latter demonstrated beneficial effects of magnesium on myocardial stunning, albeit in the presence of isoflurane (which would have affected their results). Our results showed that reversible post-ischaemic regional myocardial dysfunction persisted for at least 30 minutes after initiation of reperfusion if no additional magnesium was administered. In contrast, the addition of magnesium abolished stunning within 5 minutes after the onset of reperfusion.

Diastolic dysfunction also occurs during reperfusion.[42] Przyklenk *et al.*[43] demonstrated significant diastolic 'stunning' in a dog model after 15 minutes' occlusion of the LAD artery. The degree of diastolic dysfunction correlated significantly with the recorded systolic stunning, suggesting a common mechanism. In our study, diastolic function recovered more slowly in the presence of magnesium. This is reflected by the PSS, which rapidly returned to normal in the control group when reperfusion was started, while the magnesium group took longer to recover. In a study in isolated rat hearts, Borchgevrink and colleagues[38] demonstrated a more rapid recovery of diastolic function when magnesium was present during reperfusion, but in the study conducted by Atar *et al.*[19] the authors recorded an apparently higher end-diastolic pressure during reperfusion in the animals who received magnesium. However, this apparent difference was not statistically significant and cannot strictly be regarded as support for our findings.

Data from our experiments also demonstrated a significant increase in end-diastolic pressure for the duration of reperfusion in animals that received magnesium as opposed to those that did not receive magnesium, where the end-diastolic pressure recovered more rapidly. If the static regional end-diastolic compliance is calculated (Lmax/LVEDP) and normalised for the initial (control) step, the values were 1 for control, 0.43 ± 0.25 (X, SDM) during ischaemia and 0.49 ± 0.20, 0.68 ± 0.40 and 0.82 ± 0.70 mm/mmHg at 5, 30 and 60 minutes' reperfusion respectively. The equivalent values for the magnesium group were 0.76 ± 0.36, 0.56 ± 0.23, 0.65 ± 0.20 and 0.83 ± 0.79 mm/mmHg. These values did not differ between groups and the difference in LV end-diastolic pressures cannot, therefore, be explained by a difference in static end-diastolic chamber of muscle compliance.

The reason(s) for our observation of prolonged diastolic dysfunction in the presence of magnesium is not clear. Diastolic function is an active process and hence calcium homeostasis is involved. Lowering the calcium or administering an antagonist should decrease the availability of calcium and improve diastolic compliance. Alternatively, magnesium could cause myocardial depression resulting in an increased end-diastolic volume. However, as summarised by James,[43] previous experiments did not demonstrate significant depression of myocardial function when magnesium was administered in the same dose as used in this study. The end-systolic pressure-volume elastance (Ees), which was used in this study as an index of myocardial contractility, showed a decline in both groups after the initiation of reperfusion. However, owing to the large scatter of data and the small sample, values did not reach statistical difference when compared with control. This numerical decrease in contractility could be stunning, or a combination of stunning and a decrease in function caused by magnesium. However, in the final analysis, and irrespective of the exact mechanism, Ees was decreased to a similar degree in both groups and therefore cannot explain the difference in LVEDP as recorded. Another possible explanation is that the Lo (i.e. unstressed LV volume) increased, and if the regional shortening was similar to controls, then the Lmax (and indirectly the LVEDP) could increase. However, close inspection of our data does not support this option as Lo did not change in the magnesium group, while it was significantly increased in the control group. In addition Lmax did not change, nor did it differ between groups.

The increase in LVEDP after administration of magnesium as recorded in this and previous experiments will require further study. Our methodology and data are insufficient to forward a reasonable explanation for this observation.

These results do not allow us to be specific with regard to the mechanism of the modulating effect on the reperfusion injury, or to explain the apparent diastolic dysfunction associated with magnesium administration. One can only refer

to the known literature, which confirms that reperfusion injury is mediated by intracellular calcium overload, and that magnesium is a physiological calcium antagonist and may also limit the formation of oxygen free radicals.[44] The clinical ramification of these and the previous findings needs to be tested in a randomised fashion, with the magnesium administered either before or early during reperfusion. We are currently conducting a clinical study in which the effect of magnesium on reperfusion arrhythmias and global myocardial function is examined in patients undergoing procedures where aortic cross-clamping is required. In addition, data from the MAGIC trial,[45] which is currently underway, will also shed some light on the ability of magnesium, when administered early enough, to limit or lessen the reperfusion injury (and mortality) in 10 000 high-risk myocardial infarct patients.

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