European Heart Journal (1999) **20,** 111–120
Article No. euhj.1998.1238, available online at http://www.idealibrary.com on IDEAL

Decreases by magnesium of QT dispersion and ventricular arrhythmias in patients with acute myocardial infarction

H. Parikka, L. Toivonen, V. Naukkarinen*, I. Tierala*, S. Pohjola-Sintonen, J. Heikkilä and M. S. Nieminen

*Division of Cardiology, Helsinki University Central Hospital, Helsinki, and *Department of Medicine, Jorvi District Hospital, Espoo, Finland*

Aims Magnesium treatment suppresses ventricular arrhythmias in acute myocardial infarction and possibly mortality after infarction, but the underlying mechanisms are inadequately understood. We tested whether the effect of magnesium could be attributed to an influence on the autonomic control of the heart, changes in disturbed repolarization, relief of ischaemia or limitation of myocardial injury.

Methods and Results Fifty-nine consecutive patients with acute myocardial infarction were randomized to receive 70 mmol of magnesium (n=31) infused over 24 h or placebo (n=26). Occurrence of ventricular arrhythmias and heart rate variability (SD of 5-min mean sinus beat intervals over a 24 h period, SDANN; low frequency/high frequency amplitude ratio, LF/HF ratio), and the number of ischaemic episodes on vectorcardiography were measured from the first day of treatment. QT dispersion corrected for heart rate was measured from the 12-lead ECG. Magnesium decreased the number of hourly ventricular premature beats ($P<0{\cdot}001$) and the number of ventricular tachycardias ($P<0{\cdot}05$). QT dispersion corrected for heart rate was decreased in both measurements at 24 h and 1 week ($P<0{\cdot}001$). SDANN and LF/HF ratio were unchanged. The number of ischaemic episodes on vectorcardiography were equal, and peak creatine kinase MB release did not differ between the groups. In testing the pathophysiological mechanisms, serum magnesium levels after infusion correlated with hourly ventricular premature beats ($r_s=-0{\cdot}47$; $P<0{\cdot}01$), ventricular tachycardias ($r_s=-0{\cdot}26$; $P<0{\cdot}05$), and QT dispersion corrected for heart rate ($r_s=-0{\cdot}75$; $P<0{\cdot}001$), but not with SDANN, LF/HF ratio or peak creatine kinase MB. QT dispersion corrected for heart rate correlated with hourly ventricular premature beats ($r_s=0{\cdot}48$; $P<0{\cdot}001$) and ventricular tachycardias ($r_s=0{\cdot}27$; $P<0{\cdot}05$).

Conclusions Magnesium suppresses early ventricular arrhythmias in acute myocardial infarction. The decreased arrhythmicity is related to enhancement of homogeneity in repolarization, but not to attenuation of prevailing ischaemia, improvement of autonomic nervous derangements or myocardial salvage.
(Eur Heart J 1999; 20: 111–120)

Key Words: Magnesium, acute myocardial infarction, QT dispersion.

See page 86 for the Editorial comment on this article

Introduction

Ventricular arrhythmias are a major determinant of survival after acute myocardial infarction[1,2]. Their development is attributed to the pathophysiology of the damaged myocardium[3], and changes in the nervous regulation of the heart and ischaemia substantially modulate the generation. Myocardial infarction begets heterogeneity in repolarization and autonomic imbalance, which can non-invasively be revealed as increased spatial difference between the longest and shortest QT interval on the ECG (QT dispersion)[4], and depressed heart rate variability on an ambulatory ECG[5]. Their degree is associated with the appearance of life-threatening arrhythmias and increased mortality[5,6].

Magnesium administration has suppressed the emergence of arrhythmias[7,8] and improved survival after acute myocardial infarction[8,9], although the response has been questioned recently[10]. Magnesium

Revision submitted 3 July 1998, and accepted 12 July 1998.

Correspondence: Hannu Parikka, MD, Division of Cardiology, Helsinki University Central Hospital, PO Box 340, FIN-00029, Helsinki, Finland.

0195-668X/99/020111+10 $18.00/0

exerts a central role in the electrical stability and energy balance of the ischaemic myocyte[11], and it has the potential to affect heart rate either directly or by modifying the autonomic nervous control of the sinus node[12,13]. These properties could account for the beneficial effect.

This study investigates whether intravenous magnesium, administered in the early phase of myocardial infarction, can suppress cardiac arrhythmias. The influence on autonomic regulation of the heart rate, inhomogeneity in repolarization measured electrocardiographically as QT dispersion, ischaemia, and the extent of myocardial injury were tested as pathophysiological determinants.

Methods

Patients aged <75 years admitted to the cardiac care units of the Meilahti Hospital of the Helsinki University Central Hospital, Helsinki, Finland and Jorvi District Hospital, Espoo, Finland were screened. Fifty-nine consecutive subjects with acute myocardial infarction by ECG and/or creatine kinase MB isoenzyme criteria and <12 h from onset of chest pain were randomized to receive magnesium or placebo after informed consent was received. Patients with sick sinus syndrome, atrial fibrillation, second- or third-degree atrioventricular conduction block, insulin dependent diabetes mellitus, uncontrolled arterial hypertension, or serum creatinine concentration >250 mmol . l^{-1} were excluded. Patients with significant stenotic valve disease, permanently paced rhythm or need for immediate ventilator treatment were also considered ineligible.

Acute myocardial infarction

The criteria used for acute myocardial infarction consisted of chest pain of >20 min duration combined with ST segment elevation of $\geq$0·1 mV in $\geq$1 of the limb leads or $\geq$0·2 mV in $\geq$2 of the chest leads, or a rise in serum creatine kinase MB isoenzyme mass unit to >7 μg . l^{-1}. Creatine kinase MB was measured on admission and three times at 12 h intervals successively. The localization was considered as anterior, if the changes occurred in chest leads V_2–V_6, and inferior in leads II, III, and aVF. The acute myocardial infarction was defined as a Q wave acute myocardial infarction, if a new Q wave of $\geq$40 ms emerged. The patients received thrombolytic treatment as clinically appropriate and its start preceded the study infusion. Intravenous beta-blocker, nitrate, oral aspirin and antiarrhythmic medication were given according to the judgement of the attending clinician.

Magnesium administration

In a double blind manner, the patients received 8 mmol of 10% magnesium sulphate in 10 min followed immediately by 62 mmol in 500 ml of physiological sodium chloride infused over 24 h. The corresponding volumes of sodium chloride solution served as placebo. Blood samples for determination of serum magnesium and potassium concentrations were taken before the study treatment started and at the end of it.

Holter recording

A 24 h Holter recording was started prior to the magnesium/placebo administration. The second recording was performed prior to discharge from hospital on the 7th to 14th day, after the patient's condition had stabilized. A two-channel recorder (Marquette 8500, Marquette Electronics Inc., Milwaukee, WI, U.S.A.) was used and the tapes were analysed by the same observer with a Marquette 8000 Holter Analysis System utilizing 5.8 software. The automatic QRS classification was edited when necessary. The number of supraventricular and ventricular premature beats were calculated. Three or more consecutive supraventricular premature beats or ventricular premature beats >120 beats.min^{-1} were classified as supraventricular or ventricular tachycardias. Ventricular tachycardias <120 beats . min^{-1} were defined as slow ventricular tachycardias.

Heart rate variability was assessed by time domain and frequency domain methods from the entire 24 h recording. To calculate heart rate variability, the software uses only normal sinus beat intervals. Ectopic or artifact periods are excluded and replaced by holding the previous coupling interval level through to the next valid coupling interval. Fast Fourier Transformation was used to separate the R-R fluctuations to frequencies. The spectral bands used were 0·15–0·40 Hz (high frequency; HF) and 0·04–0·15 Hz (low frequency; LF). The spectral measures are computed as amplitudes, which are square roots of areas under power spectrum, and are presented in ms. The areas represent signal variance within frequency bands while the square root represents the standard deviation. The HF and LF components were determined from the entire 24 h recording. LF/HF amplitude ratio was calculated and used as an indicator of sympatho-vagal balance[14]. During the first recording the patients were resting but during the second they were allowed normal activity.

The standard deviation of the averaged normal-to-normal R-R intervals for all 5 min periods of the 24 h recording (SDANN) was used as the time domain method.

Electrocardiographic measurements

A standard 12-lead ECG was recorded at a paper speed of 50 mm . s^{-1} immediately on arrival at hospital (baseline), 24 h after the start of the study treatment and prior to discharge. Of these, sinus cycle length, PQ interval and QRS durations were analysed by standard criteria from lead II or V_2. QT interval was measured from the

beginning of the Q or R wave to the point where a tangent drawn along the maximal slope of the decending limb of the T wave (or ascending when the T wave was inverted) crossed the isoelectric TP baseline. If a biphasic T wave was present, the latter part was used for drawing. A separate U wave was disregarded[15]. In cases where the T wave was isoelectric or the termination of the T wave could not be reliably calculated, the lead was excluded from the analysis. QT interval measurements were calculated from three consecutive sinus beats and averaged. QT dispersion was defined as the difference between the maximal minus the minimal QT duration appearing in any of the 12 leads and corrected for heart rate according to the formula by Bazett, $QTc = QT/RR^{1/2}$[16]. At least nine analysable leads in each recording was expected. All the measurements were done blindly by the same observer.

Ischaemia detection

Continuous on-line vectorcardiography (MIDA 1000; Ortivus Medical AB, Täby, Sweden) was started 15 min before the study infusion. In MIDA, the orthogonal Frank lead system is used to compute vectorcardiography signals, which are averaged over 2-min periods. The first 2-min average period formed the reference and all changes were compared with it. The vectorcardiography parameters used were QRS vector difference, ST vector magnitude and ST change vector magnitude[17]. An ischaemic episode was defined as a reversible increase of >15 μVs in QRS vector difference from the current base level lasting >2 min, or a reversible increase of >0·1 mV in ST vector magnitude or ST change vector magnitude[17].

An ischaemic event on Holter was defined as ST depression of ≥1 mm measured 80 ms after the J point, lasting for ≥1 min and at least 1 min apart.

A symptom-limited bicycle exercise test using 3-min steps and 25 W workload increments was performed prior to discharge. ST depression of ≥1 mm measured 80 ms after the J point was defined as ischaemia.

Other measurements

Prior to discharge, echocardiographic left ventricular end-diastolic diameter and ejection fraction, high resolution signal averaged electrocardiograms and arterial baroreflex sensitivity were recorded.

In signal average electrocardiogram measurements, the total filtered QRS duration, the root-mean-square voltage in the terminal 40 ms and the duration of high frequency low amplitude signals below 40 μV were calculated (Marquette Electronics MAC-12/15, Milwaukee, WI, U.S.A.). Criteria for a positive late potential included QRS duration >110 ms, root-mean-square voltage <25 mV and high frequency low amplitude duration >35 ms. The mean ± SD noise voltage was 0·6 ± 0·3 μV.

Table 1 Demographic data. The values are median (range), or numbers (percentage). The groups were statistically equal

	Magnesium (n=31)	Control (n=26)
Age (years)	60 (30–73)	59 (36–74)
Male sex	26 (84)	22 (85)
Prior AMI	3 (10)	3 (12)
Prior beta-blocker	6 (20)	6 (23)
Prior aspirin	1 (3)	1 (4)
Diabetes	2 (6)	2 (8)
Hypertension	7 (23)	6 (23)

AMI=acute myocardial infarction.

Baroreflex sensitivity was assessed by plotting each beat-to-beat R-R interval against the preceding systolic arterial pressure obtained by invasive recording, using an intravenous 0·1 mg phenylephrine bolus increased in steps of 0·05 mg until an anticipated 15–40 mmHg rise in systolic pressure was observed[18]. The mean of three slopes of linear regression lines with a correlation coefficient ≥0·8 was defined as the baroreflex sensitivity index ($ms \cdot mmHg^{-1}$). Data recording and analysis was performed with a specified software package (Cafts, Medikro Oy, Finland).

Serum creatinine concentration was measured on admission and data concerning various patient characteristics were recorded.

The investigational protocol was approved by the Ethical Committee of Human Research of the Department of Medicine in Helsinki University.

Statistics

Group differences between continuous variables were analysed with the Mann–Whitney U test. Serial changes within the groups were analysed with the Wilcoxon signed-rank test or Friedman statistics. Bonferroni correction was applied in multiple comparisons. The data are expressed as median and range. The chi square or the Fisher's exact test was used to compare categoric variables. Correlation between variables was tested with the Spearman rank correlation test. All comparisons are two-tailed and the significance level was set at P value <0·05.

Results

The baseline characteristics were well balanced in the study groups (Table 1). The infusion caused the plasma magnesium concentration to rise to 1·30 $mmol \cdot l^{-1}$ (1·11–1·74 $mmol \cdot l^{-1}$) in the magnesium patients but it fell to 0·74 $mmol \cdot l^{-1}$ (0·61–0·92 $mmol \cdot l^{-1}$) in the controls (P<0·001 between the groups).

Table 2 Clinical profile and treatment of the acute myocardial infarction during the first 24 h. Values are median (range) or numbers (percentage)

	Magnesium (n=31)	Control (n=26)
Anterior Q wave AMI	16 (52)	6 (23)*
Inferior Q wave AMI	9 (29)	14 (54)*
Thrombolytic treatment	28 (90)	23 (88)
Time to thrombolytic treatment (h)	2·0 (1–9)	3·5 (0·5–9)
Time to study medication (h)	8 (5·5–12)	9 (5–12)
Intravenous beta-blocker	16 (52)	12 (46)
Aspirin	25 (81)	22 (85)
Serum Mg baseline (mmol . l^{-1})	0·78 (0·61–0·93)	0·78 (0·66–0·99)
Serum Mg 24 h (mmol . l^{-1})	1·30 (1·11–1·74)	0·74 (0·61–0·92)***
Serum K baseline (mmol . l^{-1})	3·90 (3·50–4·50)	4·00 (2·80–5·10)
Serum K 24 h (mmol . l^{-1})	4·10 (3·50–4·70)	4·00 (3·50–5·00)
Peak CK-MB (μg . l^{-1})	113 (7–1106)	181 (12–639)

AMI=acute myocardial infarction; CK-MB=creatine kinase MB.
*P<0·05; ***P<0·001.

Table 3 Ventricular arrhythmias. Values are median (range)

	First 24 h		At discharge	
	Magnesium (n=30)	Control (n=24)	Magnesium (n=26)	Control (n=18)
Mean sinus rate (beats . min^{-1})	72 (57–97)	70 (50–97)	66 (58–87)	68 (49–79)
VPB . h^{-1}	6 (0–115)	29 (1–469)***	0 (0–6)	1 (0–130)*
Number of couplets VPBs	3 (0–163)	13 (0–528)*	0 (0–2)	0 (0–16)
Number of R-on-T VPBs	0 (0–4)	1 (0–89)**	0 (0–15)	0 (0–7)
Number of slow VTs	0 (0–86)	4 (0–664)*	0 (0–0)	0 (0–1)
Number of VTs	1 (0–38)	5 (0–248)*	0 (0–1)	0 (0–0)

VPB=ventricular premature beats; R-on-T=ventricular premature beat appearing on the T wave; VT=ventricular tachycardia.
*P<0·05; **P<0·01; ***P<0·001 between the groups.

Infarction characteristics

The acute myocardial infarction data are summarized in Table 2. Non-Q wave acute myocardial infarction was equally distributed between the groups but anterior Q wave acute myocardial infarction was more prevalent in the magnesium patients than the controls. Time from onset of thrombolytic treatment to onset of the study treatment was 5·3 h (1–10·5 h) in the magnesium group and 5·0 h (2–10 h) in the control group (ns). Radiological left ventricular failure developed in seven (23%) and in six (23%) of the patients in the magnesium and control groups, respectively (ns). During the study period, diuretics and angiotensin converting enzyme inhibitors were given comparably. Three patients, all in the control group, experienced conduction disturbances: one persistent grade I atrioventricular block, one persistent left anterior hemiblock and one temporary grade II atrioventricular block of Wenckebach type. An episode of atrial fibrillation developed in five (16%) of the magnesium patients and in two (8%) of the controls. Sustained ventricular tachycardia was not observed.

Arrhythmias

During the first 24 h on Holter, magnesium treatment reduced the incidence of hourly ventricular premature beats, ventricular premature beat appearing on the T wave, ventricular couplets, and ventricular tachycardia episodes (Table 3). At discharge, the incidence of hourly ventricular premature beats were reduced. There was no difference in supraventricular arrhythmias, and none of the patients had sustained ventricular tachycardia or ventricular fibrillation.

Heart rate variability

SDANN or LF/HF ratio did not differ in either recording. HF amplitude was lower in the magnesium group (Table 4).

Electrocardiographic data

Table 5 summarizes the electrocardiographic data. Sinus cycle length, QT duration, QT corrected for heart rate

Table 4 Heart rate variability. Data are median (range)

	First 24 h		At discharge	
	Magnesium (n=30)	Control (n=24)	Magnesium (n=26)	Control (n=18)
Mean RR interval (ms)	829 (615–1059)	864 (614–1191)	908 (682–1035)	865 (755–1229)
SDANN (ms)	66 (30–148)	67 (38–135)	96 (35–183)	86 (54–159)
HF (ms)	7 (2–22)	13 (4–59)**	8 (4–179)	11 (4–33)
LF/HF ratio	1·9 (0·9–3·3)	1·8 (1·0–2·4)	2·2 (0·9–3·0)	1·8 (0·8–3·0)

SDANN=standard deviation of averaged normal-to-normal R-R intervals; HF/LF=high/low frequency.
**$P<0·01$ between the treatment groups.

duration, PQ interval (figures not shown) and QRS duration (figures not shown) did not differ at any measurement point between the groups. QT dispersion corrected for heart rate was significantly lower in the magnesium patients throughout the study period. Although QT dispersion corrected for heart rate seemed to increase (though not statistically) during evolving acute myocardial infarction in the controls, it decreased in the magnesium patients ($P<0·05$). Patients who had QT dispersion corrected for heart rate ≥ 100 ms at 24 h (n=12) were detected in the control group only ($P<0·001$).

Ischaemia features

In vectorcardiography, 18 (58%) of the magnesium patients and 10/23 (43%) of the controls had at least one episode of ischaemia (ns). The number of episodes in these patients was two (1–13) and three (1–12), respectively (ns).

During the first 24 h on Holter, six (19%) of the magnesium patients and two (8%) of the controls had 17 (2–32) and seven (3–11) episodes of ischaemia, respectively (ns). At discharge, the corresponding incidences were 3/18 (17%) and 2/12 (17%) and the number of episodes 24 (4–37) and 18 (9–27), respectively (ns).

Peak creatine kinase MB release or ischaemia on an exercise test did not differ between the groups. An emergency coronary angiography was performed in seven (23%) of the magnesium patients and in two (8%) of the controls (ns). Of these, six in the former and all in the latter led to PTCA or CABG later during hospitalization.

Other measurements

On echocardiography, the left ventricular end-diastolic diameter was 52 mm (39–59 mm) in the magnesium patients and 54 mm (44–71 mm) in the controls (ns). The left ventricular ejection fraction did not differ between the groups: 57% (23–76%) in the magnesium patients and 53% (27–76%) in the controls (ns).

The signal averaged electrocardiograms were registered in 48 patients. A positive late potential was detected in 7/28 (25%) of the magnesium patients and in 6/20 (30%) of the controls (ns). The baroreflex sensitivity index could be determined in 34 patients (20 magnesium patients and 14 controls). The groups did not differ: 6·6 ms . $mmHg^{-1}$ (1·0–14·6 ms . $mmHg^{-1}$) in the magnesium patients and 4·0 ms . $mmHg^{-1}$ (2·0–22·0 ms . $mmHg^{-1}$) in the controls (ns).

Relationship to acute myocardial infarction site

Ventricular arrhythmias were equally distributed whether the acute myocardial infarction was anterior or inferior. Furthermore, acute myocardial infarction location did not affect QT dispersion corrected for heart

Table 5 Electrocardiographic data. The values are median (range)

	Baseline		24 h		At discharge	
	Magnesium (n=31)	Control (n=26)	Magnesium (n=30)	Control (n=26)	Magnesium (n=28)	Control (n=25)
Sinus cycle length (ms)	770 (560–1420)	805 (585–1150)	860 (580–1080)	850 (570–1290)	920 (600–1350)	975 (710–1230)
QTc mean (ms)	409 (344–464)	419 (373–481)	445 (285–546)	429 (390–494)	404 (352–442)	397 (352–481)
QTcD (ms)	76 (11–108)	78 (31–141)	50 (14–88)	97 (49–166)***	41 (19–75)	67 (24–107)***

QTc=QT duration corrected for heart rate; QTcD=QT dispersion corrected for heart rate.
***$P<0·001$ between the groups.

Table 6 Influence of infarct site on the effect of Mg during the first 24 h. Values are median (range) or numbers (percentage)

	Anterior AMI		Inferior AMI	
	Magnesium (n=16)	Control (n=6)	Magnesium (n=9)	Control (n=14)
VPB . h^{-1}	12 (0–115)	149 (8–264)*	6 (0–59)	29 (1–125)*
Number of VTs	3 (0–21)	9 (0–65)	2 (0–38)	5 (0–66)
QTcD (ms)	53 (32–69)	107 (75–166)***	42 (14–52)	97 (61–142)***
SDANN (ms)	58 (30–110)	60 (38–91)	83 (59–148)	73 (40–135)
LF/HF ratio	1·9 (0·9–2·8)	1·6 (1·3–2·1)	2·0 (1·4–3·3)	1·9 (1·2–2·4)
Number of patients with ischaemia on VCG	6 (38)	4 (67)	8 (89)	6 (50)
Peak CK-MB ($\mu g . l^{-1}$)	187 (7–1106)	144 (44–639)	44 (20–538)	186 (25–357)*

VCG=vectorcardiography; for other abbreviations, see earlier tables.
*P<0·05; **P<0·01; ***P<0·001.

rate, LF/HF ratio, ischaemia on the two Holter recordings, vectorcardiography or exercise test. The patients who had an anterior Q wave acute myocardial infarction had greater peak creatine kinase MB levels (175 IU (7–1106 IU) vs 97 IU (9–538 IU); P<0·05), and a lower SDANN (P<0·05) and HF amplitude (P<0·01) on the first 24 h Holter recording but not at discharge, than the patients with an inferior acute myocardial infarction.

Among the patients with an anterior Q wave acute myocardial infarction, QT dispersion corrected for heart rate throughout the study period, the incidences of hourly ventricular premature beats, and ventricular premature beats appearing on the T-wave (P<0·05) during the first 24 h were reduced in the magnesium patients compared to the controls. Heart rate variability, ischaemia or peak creatine kinase MB did not differ between the study groups (Table 6). Among the patients with an inferior Q wave acute myocardial infarction, QT dispersion corrected for heart rate throughout the study period, and hourly ventricular premature beats during the first 24 h were lower in the magnesium patients compared to the controls. Heart rate variability and ischaemia did not differ, but peak creatine kinase MB release was lower in the magnesium patients (Table 6).

Associates of ventricular arrhythmias

There was an association between the appearance of ventricular arrhythmias during the first 24 h, serum magnesium concentration, and QT dispersion corrected for heart rate: serum magnesium concentration after the infusion correlated negatively with hourly ventricular premature beats ($r_s = -0·47$; P<0·01), the number of couplet ventricular premature beats ($r_s = -0·29$; P<0·05), and the number of ventricular tachycardias ($r_s = -0·26$; P<0·05). QT dispersion corrected for heart rate at 24 h correlated with hourly ventricular premature beats (r_s=0·48; P<0·001) and the number of ventricular tachycardias (r_s=0·27; P<0·05). The patients with QT dispersion corrected for heart rate $\geq$100 ms at 24 h had more ventricular tachycardias (P<0·05) and hourly ventricular premature beats (P<0·01) during the first 24 h than the patients with QT dispersion corrected for heart rate <100 ms. No correlation was found between the appearance of ventricular arrhythmias and any of the heart rate variability parameters, transient ischaemia on vectorcardiography, or the early use of intravenous beta-blockers.

Other relationships

QT dispersion corrected for heart rate at 24 h was strongly inversely correlated with serum magnesium concentration after the infusion ($r_s = -0·75$ respectively; P<0·001) (Fig. 1). There was also a negative correlation between serum magnesium concentration and HF ($r_s = -0·45$; P<0·01), but not between magnesium and the LF/HF ratio or SDANN during the first 24 h. In patients with transient ischaemia on vectorcardiography (n=28) or Holter (n=8) during the first 24 h, QT dispersion corrected for heart rate did not differ from the patients free of ischaemia. QT dispersion corrected for heart rate measurement did not necessarily coincide with the appearance of the ischaemia indeces.

Discussion

The main findings in the present study are suppression of ventricular arrhythmias and a decrease in QT dispersion in patients treated with magnesium in the early phase of acute myocardial infarction. Effects on autonomic nervous balance, ischaemia, or extent of myocardial damage were not found. A pathophysiological link between magnesium treatment, decreased QT dispersion and decreased incidence of ventricular arrhythmias may be suggested on the basis of the interrelationship between these factors.

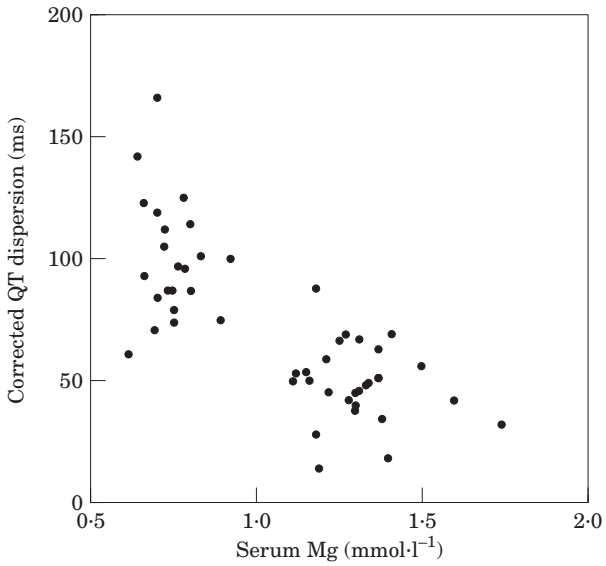

Figure 1 **The association between serum Mg level and corrected QT dispersion at 24 h, assessed by the Spearman rank correlation test. $r_s = -0{\cdot}75$; $P<0{\cdot}001$.**

Magnesium and ventricular arrhythmias in acute myocardial infarction

The ventricular arrhythmia reduction in the present study was substantial during the magnesium infusion, suggesting a true treatment effect. In other studies evaluating the first 24 h effect, Abraham *et al.* showed a reduction in ventricular arrhythmias from 34·8% to 14·6%[19]. The LIMIT-2 study noticed no suppression in clinically documented peri-infarct arrhythmias. Similar result was evident in a Holter substudy of 48 patients[9,20]. Thögersen *et al.* found only a tendency towards a reduction in episodes of repetitive ventricular premature complexes[21]. Applying longer detection periods, Rasmussen *et al.* reported a decrease from 47% to 21% in the incidence of arrhythmias requiring treatment during the initial week of hospitalization[7]. In ISIS-4, the largest trial assessing magnesium's effect in acute myocardial infarction, fewer patients with magnesium treatment experienced ventricular fibrillation during hospitalization, without consequent implications on overall mortality[10]. Combining the heterogenous arrhythmia definitions, registration periods, and administration protocols, the meta-analysis of small-scale trials by Horner revealed a 49% reduction in the incidence of ventricular tachycardia and fibrillation by magnesium treatment[8]. Although magnesium dosing in our study corresponds with that in LIMIT-2, the responses differ. A higher proportion of our patients treated with thrombolytics (~90% vs ~36%) and later onset of magnesium administration might contribute to the difference.

Magnesium and QT dispersion in acute myocardial infarction

Our data demonstrate that the early increase in QT dispersion, known to follow acute myocardial infarction[4,22], is abolished by magnesium treatment and the effect is maintained for up to one week. The response is not attributed to alterations in QT or QT corrected for heart rate durations, which remained comparable between the treatment groups. This is in agreement with previous findings that QT dispersion is not related directly to QT duration, and interventions that prolong QT duration do not implicitly increase QT dispersion[23]. Furthermore, magnesium has not been found to alter the electrocardiographic QT interval in healthy subjects[12].

Spatial QT dispersion is recognized as a marker of regional inhomogeneity in ventricular refractoriness, prominent in the border zone between non-ischaemic and ischaemic myocardium[24], and thus, a substrate for re-entrant ventricular tachyarrhythmias[25–27]. Repolarization can be modified by the ischaemic process itself[28], changes in the nervous regulation of the heart[29], and some pharmacochemical interventions[23,30]. While transient ischaemia, peak creatine kinase MB release, and heart rate variability measures were not associated with the degree of QT dispersion, serum magnesium levels were, suggesting that magnesium was a major determinant of homogenous repolarization.

The benefit following magnesium treatment was still recognizable at one week, implying that magnesium might induce long-term modifications in the evolving arrhythmia substrate. Among patients with acute myocardial infarction, excessive dispersion in repolarization detected at discharge has predicted increased susceptibility to later life-threatening ventricular arrhythmias or sudden death[6,27], but not within the first 3 days[31].

Magnesium and autonomic control of heart in acute myocardial infarction

Magnesium exerted no influence on the sympathovagal balance either in the early phase or at discharge, as demonstrated by the unchanged SDANN or LF/HF ratio. The early decrease in HF amplitude in the magnesium patients probably reflects the anterior acute myocardial infarction dominance in these patients, since anterior acute myocardial infarctions were associated with lower HF amplitude, as also shown in other groups[29,32]. Furthermore, baroreflex sensitivity was not influenced by magnesium treatment. It has been shown that impairment of cardiac neural function occurs within minutes after cessation of coronary blood flow and reversibility is only achieved with rapid interventions[33]. Relatively late administration of magnesium after onset of symptoms and thrombolytic treatment may have failed to save the function of autonomic innervation within myocardium. As blunted heart rate variability

and baroreflex sensitivity after acute myocardial infarction are powerful, independent estimators of survival and malignant ventricular arrhythmias[6,34,35], the observed neutral effect lessens the probability of magnesium's modifying the prognosis via changes in autonomic control of the heart.

Magnesium, ischaemia and acute myocardial infarction size

Dynamic vectorcardiographic monitoring is a sensitive non-invasive method of identifying recurrent myocardial ischaemia and vessel patency in association with acute myocardial infarction[17,36] and of estimating prognosis after acute myocardial infarction[37]. Although experimental data promotes magnesium's anti-ischaemic[11,38,39] and reperfusion injury reducing[40–42] properties, early ischaemia suppression could not be verified in our study. It is concluded, that despite the reduction in ischaemia in patients with unstable angina following magnesium[43], it cannot restrict early residual ischaemia once infarction has emerged (ISIS-4; our data). Furthermore, the extent of myocardial damage, assessed by cardiac enzyme release, left ventricular dimensions and function, or appearance of late potentials, was not diminished. This is consistent with in vivo studies that show infarct size limitation only if magnesium administration is initiated before or at the time of reperfusion[40,41].

Determinants behind arrhythmia suppression

The diminished arrhythmicity was closely ascribed to magnesium's ability to decrease QT dispersion. This association has not been noticed earlier. In general, while QT dispersion has identified patients at increased risk for arrhythmic death, the connection between decreased QT dispersion and suppression of ventricular arrhythmias has not been confirmed in acute myocardial infarction patients previously[44].

Under experimental ischaemia, magnesium has the potential to modify repolarization. Magnesium is a co-factor of several membrane-bound ion pumps and a regulator of some ion channels operating during repolarization of the myocyte[11]. Apart from anti-ischaemic action[11,38,42,43], restoration of the electrochemical gradient across the sarcolemma, induced mainly by potassium and calcium fluxes secondary to ischaemia[11,45–48], has been shown. Accordingly, the ischaemia-induced early prolongation of the epicardial monophasic action potential duration is shortened by magnesium[49]. Based on the present clinical data, it may be assumed that the primary magnesium action is to modify the unstable electrical environment, not to alleviate ischaemia. This gains support from the observation that magnesium acted electrically, i.e. reduced arrhythmias, and not by diminishing infarction. Secondly, dispersion in repolarization reflects conditions in the electrophysiological substrate for ventricular arrhythmias[24,26,50]. Thirdly, regarding the dependence of QT dispersion on the location (present study) and the extent of infarct[28], magnesium's influence was independent of these (Table 6).

The reduction in QT dispersion, a marker of a re-entrant arrhythmia mechanism, explains inaccurately the decrease in the incidence of ventricular ectopic beats, that are considered an expression of increased excitability due to acute ischaemia[51]. Whether true re-entrant ventricular arrhythmias, sustained ventricular tachycardias, are also prevented by magnesium could not be judged.

Clinical implications

The arrhythmia reduction was obvious during the early hospitalization. While arrhythmia reduction has improved in-hospital[52] and long-term prognosis[8,53] in small studies, LIMIT-2 did not raise this mechanism to explain the reduced mortality[9,20]. In the absence of robust end-points (sustained ventricular tachycardia, ventricular fibrillation, and death), and regarding the mechanistic, not prognostic nature of the present study, caution is warranted in estimating the clinical significance of the observed arrhythmia suppression on morbidity or mortality. However, increased frequency of hourly ventricular premature beats at discharge after acute myocardial infarction has also predicted adverse outcome under thrombolysis[2,54]. Increased homogeneity in repolarization, demonstrated to last through the recovery phase, would be assumed to protect against generation of life-threatening ventricular arrhythmias or sudden death. The deviating influence of magnesium treatment on the prognostic markers may partly explain the discrepant outcomes in the studies evaluating magnesium's effect on survival after acute myocardial infarction.

Conclusions

The present study demonstrates that intravenous magnesium administered in the early phase of acute myocardial infarction attenuates the incidence of ventricular arrhythmias. The reduced arrhythmicity by magnesium is closely linked to enhancement in homogeneity of repolarization, but not to improvement of autonomic regulation of heart, alleviation of ischaemia, or myocardial salvage.

We thank P. Kettunen, MD, J. Rapola, MD, and R. Sipilä, MD, for their valuable contribution to the study. This study was supported by the Aarne Koskelo foundation.

References

[1] Bigger JT, Weld FM, Rolnitzky LM. Prevalence, characteristics and significance of ventricular tachycardia (three or more

complexes) detected with ambulatory electrocardiographic recording in the late hospitalization phase of acute myocardial infarction. Am J Cardiol 1981; 48: 815–23.
[2] Statters DJ, Malik M, Redwood S, Hnatkova K, Staunton A, Camm AJ. Use of ventricular premature complexes for risk stratification after acute myocardial infarction in the thrombolytic era. Am J Cardiol 1996; 77: 133–8.
[3] Mont L, Cinca J, Blanch P *et al*. Predisposing factors and prognostic value of sustained monomorphic ventricular tachycardia in the early phase of acute myocardial infarction. J Am Coll Cardiol 1996; 28: 1670–6.
[4] Mirvis DM. Spatial variation of QT intervals in normal persons and patients with acute myocardial infarction. J Am Coll Cardiol 1985; 5: 624–31.
[5] Kleiger RE, Miller JP, Bigger JT, Moss AJ, and the Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987; 59: 256–62.
[6] Zareba W, Moss AJ, le Cessie S. Dispersion of repolarization and arrhythmic cardiac death in coronary artery disease. Am J Cardiol 1994; 74: 550–3.
[7] Rasmussen HS, Norregard P, Lindenberg O *et al*. Intravenous magnesium in acute myocardial infarction. Lancet 1986; I: 234–6.
[8] Horner SM. Efficacy of intravenous magnesium in acute myocardial infarction in reducing arrhythmias and mortality. Meta-analysis of magnesium in acute myocardial infarction. Circulation 1992; 86: 774–9.
[9] Woods KL, Fletcher S, Roffe C, Haider Y. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). Lancet 1992; 339: 1553–8.
[10] ISIS-4 Collaborative Group. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. Lancet 1995; 345: 669–85.
[11] White RE, Hartzell HC. Magnesium ions in cardiac function. Regulator of ion channels and second messengers. Biochem Pharmacol 1989; 38: 859–67.
[12] DiCarlo Jr LA, Morady F, De Buitleir M, Krol RB, Schurig L, Annesley TM. Effects of magnesium sulfate on cardiac conduction and refractoriness in humans. J Am Coll Cardiol 1986; 7: 1356–62.
[13] Somjen GG, Baskerville EN. Effect of excess magnesium on vagal inhibition and acetylcholine sensitivity of the mammalian heart in situ and in vitro. Nature 1968; 217: 679–80.
[14] Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996; 17: 354–81.
[15] Lepeschkin E, Surawicz B. The measurement of the Q-T interval of the electrocardiogram. Circulation 1952; 6: 378–88.
[16] Bazett HC. An analysis of the time relationships of the heart. Heart 1920; 7: 353–70.
[17] Lundin P, Eriksson SV, Erhardt L, Strandberg L-E, Rehnqvist N. Continuous vectorcardiography in patients with chest pain indicative of acute ischemic heart disease. Cardiology 1992; 81: 145–56.
[18] Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man: A quantative method of assessing baroreflex sensitivity. Circ Res 1969; 24: 109–21.
[19] Abraham AS, Rosenmann D, Kramer M *et al*. Magnesium in the prevention of lethal arrhythmias in acute myocardial infarction. Arch Intern Med 1987; 147: 753–5.
[20] Roffe C, Fletcher S, Woods KL. Investigation of the effects of intravenous magnesium sulphate on cardiac rhythm in acute myocardial infarction. Br Heart J 1994; 71: 141–5.
[21] Thögersen AM, Johnson O, Wester PO. Effects of intravenous magnesium sulphate in suspected acute myocardial infarction on acute arrhythmias and long-term outcome. Int J Cardiol 1995; 49: 143–51.
[22] Higham PD, Furniss SS, Campbell RWF. QT dispersion and components of the QT interval in ischaemia and infarction. Br Heart J 1995; 73: 32–6.
[23] Day CP, McComb JM, Matthews J, Campbell RW. Reduction in QT dispersion by sotalol following myocardial infarction. Eur Heart J 1991; 12: 423–7.
[24] Schneider CA, Voth E, Baer FM, Horst M, Wagner R, Sechtem U. QT dispersion is determined by the extent of viable myocardium in patients with chronic Q-wave myocardial infarction. Circulation 1997; 96: 3913–20.
[25] Kurz RW, Ren XL, Franz MR. Dispersion and delay of electrical restitution in the globally ischaemic heart. Eur Heart J 1994; 15: 547–54.
[26] Kuo CS, Reddy CP, Munakata K, Surawicz B. Mechanism of ventricular arrhythmias caused by increased dispersion of repolarization. Eur Heart J 1985; 6: 63–70.
[27] Pye M, Quinn AC, Cobbe SM. QT interval dispersion: a non-invasive marker of susceptibility to arrhythmia in patients with sustained ventricular arrhythmias. Br Heart J 1994; 71: 511–4.
[28] Moreno FL, Villanueva MT, Karagounis LA, Anderson JL, for the TEAM-2 study investigators. Reduction in QT interval dispersion by successful thrombolytic therapy in acute myocardial infarction. Circulation 1994; 90: 94–100.
[29] Singh N, Mironov D, Armstrong PW, Ross AM, Langer A,; for the GUSTO ECG Substudy Investigators. Heart rate variability assessment early after acute myocardial infarction. Circulation 1996; 93: 1388–95.
[30] Choy AM, Lang CC, Chomsky DM, Rayos GH, Wilson JR, Roden DM. Normalization of acquired QT prolongation in humans by intravenous potassium. Circulation 1997; 96: 2149–54.
[31] Glancy JM, Garratt CJ, Woods KL, de Bono DP. QT dispersion and mortality after myocardial infarction. Lancet 1995; 345: 945–8.
[32] Lombardi F, Sandrone G, Spinnler MT *et al*. Heart rate variability in the early hours of an acute myocardial infarction. Am J Cardiol 1996; 77: 1037–44.
[33] Zipes DP. Influence of myocardial ischemia and infarction on autonomic innervation of heart. Circulation 1990; 82: 1095–105.
[34] Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992; 85: 164–71.
[35] La Rovere MT, Specchia G, Mortara A, Schwartz PJ. Baroreflex sensitivity, clinical correlates, and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. Circulation 1988; 78: 816–24.
[36] Dellborg M, Steg PG, Simoons M *et al*. Vectorcardiographic monitoring to assess early vessel patency after reperfusion therapy for acute myocardial infarction. Eur Heart J 1995; 16: 21–9.
[37] Lundin P, Eriksson SV, Strandberg L-E, Rehnqvist N. Prognostic information from on-line vectorcardiography in acute myocardial infarction. Am J Cardiol 1994; 74: 1103–8.
[38] Vigorito C, Giordano A, Ferraro P *et al*. Hemodynamic effects of magnesium sulfate in the normal human heart. Am J Cardiol 1991; 67: 1435–7.
[39] Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, Nishio A. $Mg^{2+} - Ca^{2+}$ interaction in contractility of vascular smooth muscle: Mg^{2+} versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. Can J Physiol Pharmacol 1987; 65: 729–45.
[40] Herzog WR, Schlossberg ML, MacMurdy KS *et al*. Timing of magnesium therapy affects experimental infarct size. Circulation 1995; 92: 2622–6.
[41] Christensen CW, Rieder MA, Silverstein EL, Gencheff NE. Magnesium sulphate reduces myocardial infarct size when

administered before but not after coronary reperfusion in a canine model. Circulation 1995; 92: 2617–21.
[42] Ferrari R, Albertini A, Curello S *et al*. Myocardial recovery during post-ischaemic reperfusion: effects of nifedipine, calcium and magnesium. J Mol Cell Cardiol 1986; 18: 487–98.
[43] Redwood SR, Bashir Y, Huang J, Leatham EW, Kaski J-C, Camm AJ. Effect of magnesium sulphate in patients with unstable angina. A double blind, randomized, placebo-controlled study. Eur Heart J 1997; 18: 1269–77.
[44] Davey PP, Bateman J, Mulligan IP, Forfar C, Barlow C, Hart G. QT interval dispersion in chronic heart failure and left ventricular hypertrophy: relation to autonomic nervous system and Holter tape abnormalities. Br Heart J 1994; 71: 268–73.
[45] Weiss J, Shine KI. Extracellular potassium accumulation during myocardial ischemia: implications for arrhythmias. J Mol Cell Cardiol 1994; 13: 699–704.
[46] Kraft LF, Katholi RE, Woods WT, James TN. Attenuation by magnesium of the electrophysiologic effects of hyperkalemia on human and canine heart cells. Am J Cardiol 1980; 45: 1189–95.
[47] Kline RP, Hanna MS, Dresdner KP, Wit AL. Time course of changes in intracellular K^+, Na^+ and pH of subendocardial Purkinje cells during the first 24 hours after coronary occlusion. Circ Res 1992; 70: 566–75.
[48] Kiyosue T, Arita M. Magnesium restores high K-induced inactivation of the fast Na channel in guinea pig ventricular muscle. Pflugers Arch 1982; 395: 78–80.
[49] Redwood SR, Taggart PI, Sutton PM *et al*. Effect of magnesium on the monophasic action potential during early ischemia in the in vivo human heart. J Am Coll Cardiol 1996; 28: 1765–9.
[50] Janse M, Wit A. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. Physiol Rev 1989; 69: 1049–69.
[51] Pucheu A, Lacroix H, Tonet JL, Frank R, Fontaine G, Grosgogeat Y. Ventricular arrhythmias. Cellular electrophysiological mechanisms of arrhythmias. In: Macfarlane PW, Lawrie TDV, eds. Comprehensive Electrocardiology. Theory and practice in health and disease. Pergamon Press, Oxford, England 1989: 962–5.
[52] Rasmussen HS, Gronbaek M, Cintin C, Balslov S, Norregard P, McNair P. One-year death rate in 270 patients with suspected acute myocardial infarction, initially treated with intravenous magnesium or placebo. Clin Cardiol 1988; 11: 377–81.
[53] Schecter M, Hod H, Chouraqui P, Kaplinsky E, Rabinowitz B. Magnesium therapy in acute myocardial infarction when patients are not candidates for thrombolytic therapy. Am J Cardiol 1995; 75: 321–3.
[54] Maggioni AP, Zuanetti G, Franzosi MG *et al*. on behalf of GISSI-2 investigators. Prevalence and prognostic significance of ventricular arrhythmias after acute myocardial infarction in the fibrinolytic era. GISSI-2 results. Circulation 1993; 87: 312–22.