Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 2000; 3 (2), 123-128

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Jeremias A, Bertschat FL, Ising H, Jeremias E

Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

Possible Correlation between Decrease of Ionized Magnesium and Calcium in Blood to Patient Outcome after Acute Myocardial Infarction

A. Jeremias, F. L. Bertschat, E. Jeremias, H. Ising[1]

Acute myocardial infarction (MI) can result in severe complications such as ventricular arrhythmia and congestive heart failure. Contributing factors to these complications may be disturbances in the calcium and magnesium status, especially in the biologically active ionized fraction in plasma. The purpose of this prospective study was to evaluate whether changes in ionized magnesium (iMg^{2+}) and ionized calcium (iCa^{2+}) concentrations could predict the outcome after acute myocardial infarction (MI).

In a group of 33 MI patients, total and ionized plasma magnesium and calcium were measured within the first four hours after the onset of symptoms. Major adverse cardiac events (MACE) were observed during the entire hospital stay (23±5 days). For the measurement of iMg^{2+} and iCa^{2+} an ion-sensitive electrode was used and the total amounts of calcium and magnesium were measured by atomic absorption spectrometry. By logistic regression analysis indicators for developing complications after acute MI were found to be low iCa^{2+} (<1.1 mmol/l) and a low quotient between iMg^{2+} and total magnesium (QMg < 0.65; $p<0.05$). Low QMg seems to indicate a decrease of iMg^{2+} in the first hours after an acute MI. When QMg was ≥ 0.65, only 5 out of 23 (22 %) patients developed MACE, in contrast to 7 out of 10 patients (70 %) with QMg < 0.65 ($p < 0.01$). Similar results were found for iCa^{2+}: 5 out of 22 patients with $iCa^{2+} \geq 1.1$ developed MACE in contrast to 7 out of 11 patients with $iCa^{2+} < 1.1$ mmol/l ($p < 0.05$).

A low quotient between ionized and total magnesium and/or low iCa^{2+} in blood plasma are correlated to MACE after acute MI. Low iCa^{2+} seems to be a risk factor for congestive heart failure while low QMg seems to indicate an increased risk of both congestive heart failure and arrhythmia after acute MI. *J Clin Basic Cardiol 2000; 3: 123-7.*

Key words: acute myocardial infarction, ionized magnesium, total magnesium, ionized calcium, complications after acute myocardial infarction

Although new therapeutic strategies have led to a considerable decline in deaths due to acute myocardial infarction (MI), the development of complications after acute MI is still substantial [1]. Whether the intravenous (i.v.) application of magnesium in the acute phase has a role in the therapeutic management is still a matter of controversy. While i.v. magnesium in the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) showed a favourable outcome [2], it had no beneficial effect in the fourth International Study of Infarct Survival (ISIS-4) [3]. Therefore, magnesium infusions after acute MI are not recommended as a standard therapy [4].

Another issue of discussion is whether serum magnesium is lowered in patients with acute MI and whether a decrease of serum magnesium during acute MI is correlated to the outcome and complication rate. Some studies indicate that chronic stress leads to magnesium loss [5] particularly for magnesium in bones [6] and intracellular regions, ie, heart muscles cells [7]. Acute stress like noise exposure has been shown to lead to acute release of magnesium via increased catecholamines [8]. Chronic stress in combination with low magnesium intake was shown to lead to a depletion of magnesium and intracellular calcium/magnesium shifts [9]. These alterations increase the stress sensitivity by a reduced release of magnesium during acute stress. It has been shown that the same noise exposure causes much stronger releases of catecholamines after a period of negative magnesium balance [10].

Acute myocardial infarction is a severe stressor and causes substantial catecholamine release. It was shown that a severe catecholamine increase during an acute MI is related to increased myocardial damage and an increased risk of complications after the MI [11, 12]. Since the catecholamine release during stress is increased after prolonged magnesium loss, the risk of complications after acute MI is expected to rise as well. Some studies indicate a higher prevalence of transient hypomagnesaemia in patients with acute MI [13–16], while others do not find such an association [17, 18]. To the best of our knowledge it has not yet been investigated whether complications after acute MI are correlated to ionized plasma magnesium (iMg^{2+}) which represents the biologically active form [19] and may therefore reflect more accurately the effects of magnesium.

Therefore, we modified our interaction model for stress and calcium/magnesium shifts [9] from 1986 as follows: As long as an increase of iMg^{2+} occurs during stress, (ie, acute MI), this has a stabilizing effect. If, however, during stress, iMg^{2+} is decreased because of magnesium uptake by adipocytes in combination with the above mentioned decreased magnesium release after a prolonged period of negative magnesium balance, the risk of an uncontrolled amplification of norepinephrine release, calcium influx and vasoconstriction may lead to vasospasm and an increased risk of ventricular fibrillation.

A moderate increase of iMg^{2+} during stress is the normal physiological reaction counterbalancing the stress-induced increase of the catecholamines. This last part of the above model was experimentally verified [20]. Additionally it was shown in an animal model that prolonged periods of magnesium losses caused by low magnesium intake and stress-induced high magnesium excretion will lead to a reduction of stress-induced iMg^{2+} increases [9]. In humans long term decreases of the erythrocyte magnesium have been used to demonstrate net magnesium losses [21, 22]. Net magnesium losses

Received January 14th, 1999; revision received June 15th, 1999; accepted October 8th, 1999.
From the Deptartment of Nephrology/Intensive Care, Charité Campus Virchow-Klinikum, Humboldt University, Berlin, Germany, and from the [1]Institute for Water, Soil and Air Hygiene, Federal Environmental Agency, Berlin, Germany
Correspondence to: Prof. Dr. Hartmut Ising, Federal Environmental Agency, Institute for Water, Soil and Air Hygiene, P.O. Box 33 00 22, D-14191 Berlin, Germany

are caused for example by a combination of suboptimal magnesium intake and noise stress [10, 21, 23]. Since these conditions seem to be quite common, a considerable percentage of the population may be at risk of iMg^{2+} decreases under acute stress ie, acute MI.

The special hypothesis to be tested in this paper is the described tendency of the above mentioned interaction model to become unstable under the condition that acute stress is followed by a decrease of iMg^{2+}. In that case the stress-induced increase of catecholamines is amplified and thus the risk of complications after the acute MI is increased.

On the other hand, an overreaction of iMg^{2+} increases may cause problems since magnesium is the physiological calcium antagonist. Therefore a strong increase of magnesium may decrease the calcium influx into the myocardial cells and thus increase the risk of congestive heart failure.

The aim of this study was to determine prospectively the complication rate in acute MI patients depending upon their levels of serum iMg^{2+} and iCa^{2+}, total magnesium and calcium and additionally of the quotient of these parameters.

Methods

Patient selection

Patients admitted to the medical Intensive Care Unit (ICU) of the Virchow-Hospital, Humboldt University, Berlin, Germany during a time period of 4 months with a documented acute MI (characteristic electrocardiographic signs, rise in total serum creatine kinase activity [> 1.5 times the upper reference value of our laboratory] and its myocardial isomer [MB fraction] and typical pain sensation) were prospectively entered in the database. A total of 42 patients was admitted and blood samples were taken from them all upon arrival. Careful questioning of the patients revealed that 33 of them had developed characteristic chest pain within the prior 4 hours and were, therefore, eligible for the study. The remaining 9 patients who had chest pain for more than 4 hours were excluded from further analysis.

During admission, information was obtained regarding age, gender, history of previous MI, cardiovascular risk factors (smoking, hyperlipidaemia, hypertension and diabetes mellitus) and medication. Informed consent was obtained from all patients.

Measurement of plasma electrolytes

The total plasma magnesium, total calcium, iMg^{2+} and ionized calcium (iCa^{2+}) were determined and the quotient between ionized and total magnesium was calculated for every patient. The measurement of total plasma magnesium and total plasma calcium was accomplished by atomic absorption spectrometry (IL 251, Thermo Instrument Systems GmbH). For the simultaneous measurements of plasma iMg^{2+}, iCa^{2+} and pH, ion sensitive electrodes (ISE) (Microlyte Magnesium, KONE Instruments, Espo, Finland) were used as previously described [19]. Blood gas analysis was performed immediately after venous puncture and the pH_0 (time of blood sampling) of the whole blood sample was determined. Thereafter, plasma samples were prepared using tubes with Na^+-heparin (concentration 10,000–20,000 units/l) and the activities of free electrolytes were measured by the ISEs together with the pH_1 (time of electrolyte measurements) of the sample. Since iMg^{2+} and iCa^{2+} are influenced by pH (a shift towards the ionized fractions with a decline in pH and vice versa with an increase in pH), the true value for both electrolytes was calculated, based on the modified Siggaard-Andersen-equation according to the pH-shift ($\Delta pH = pH_1 - pH_0$):

$$iMg^{2+}(pH_0) = iMg^{2+}(pH_1) \star 10^{x\Delta pH},$$

for iMg^{2+} x = 0.11 and for iCa^{2+} x = 0.24 was used [19].

Using this equation for the correction of iMg^{2+} and iCa^{2+} for the pH-range between 7.0 and 7.8, the maximum error does not exceed ±10 %. A detailed discussion of the method of iMg^{2+} measurement in blood serum and plasma including the reproducibility and accuracy was published previously [19]. For further analysis the quotient between iMg^{2+} and total plasma magnesium (QMg) was calculated.

Study design

The total collective of 33 patients was divided into two groups according to their QMg as measured at admission. Group A consisted of 23 patients with QMg ≥ 0.65 and group B of 10 patients with QMg < 0.65. The cutoff-point of 0.65 was determined in a previous study [19]. Results of the magnesium determination were not available to the treating physician, and hence did not influence the overall care of the patients. All patients were treated in accordance with the usual procedures of the ICU and none of them received magnesium infusions. To ensure adequate characterization of the two study groups, data were collected on peak creatine kinase, CK-MB fractions (taken as rough indices of the extent of the MI) and the location of MI (by electrocardiography). Major adverse cardiac events (MACE) were followed in both groups for the time of hospitalization. The diagnosis of MACE was given if a patient developed serious arrhythmias (Lown class > 3) and/or congestive heart failure (systolic blood pressure < 90 mmHg and/or need for vasopressors).

Statistical analysis

Univariate correlation between the variables was performed by the Spearman rank correlation coefficient. Logistic regression analysis was carried out to test the hypothesis of a dependency of MACE upon magnesium and calcium parameters. All data are reported as mean ± SD or percentage occurrences of a variable in both groups. Group means of ratio scale variables of both groups were compared by Student's t-test and Yates corrected Chi-square analysis, as appropriate. A p-value < 0.05 was considered statistically significant.

Results

Twelve out of the 33 patients developed MACE within 23 ± 5 days after acute MI. Table 1 shows the distribution of MACE to arrhythmias (Lown ≥ 3, ventricular fibrillation and successful cardiopulmonary resuscitation, death) and congestive heart failure (hypotension, death). Calcium and magnesium concentrations and pH of 12 patents with MACE and 21 patients without MACE are shown in Table 2. In patients with MACE significant decreases were found for iCa^{2+}, iMg^{2+} and QMg whereas bound magnesium was significantly increased.

To study the relationship between MACE and electrolyte parameters Spearman correlation analysis was carried out. The results are given in Table 3. There is a significant negative correlation between QMg and the development of ventricular

Table 1. Type of major adverse cardiac events (MACE), which developed in 12 out of 33 patients within 23±5 days after acute MI

Arrhythmia	Congestive heart failure		
	No	Hypotension	Death
No	0	5	1
Lown ≥ 3	1	2	0
Ventricular fibrillation	0	2	0
Death	0	1	0

arrhythmia as well as QMg and the development of congestive heart failure. QMg proved to be a better parameter for the prediction of MACE than either total magnesium or iMg^{2+} alone. Bound magnesium was positively and nearly as closely correlated to MACE as QMg. Regarding calcium, the only significant correlation was found for iCa^{2+} and the development of congestive heart failure. The quotient between ionized and total calcium had no predictive value. Other significant variables in the univariate analysis turned out to be age and the location of the infarction. Previous infarction was significantly associated with the development of congestive heart failure and infarct size (as estimated by the creatine kinase release) was associated with ventricular arrhythmia.

Logistic regression analysis with MACE as the dependent variable and plasma electrolytes and the co-variables age and previous infarction as independent variables resulted in QMg and iCa^{2+} as significant predictors for MACE. Age and previous infarction were associated with an increase in relative risks but did not reach statistical significance. Significance and odds ratios resulting from the logistic regression analysis between MACE and electrolyte parameters as well as the mentioned co-variables are listed in Table 4. Location and size of the MI as co-variables were eliminated in early steps of the analysis.

Additional logistic regression analysis revealed significant correlations of MACE to the combination of total magnesium, iMg^{2+} and iCa^{2+} with age and re-infarction as co-variables. However, total magnesium was positively correlated to MACE. Elimination of total magnesium or iMg^{2+} lead to loss of significance of the remaining magnesium parameter but did not influence the significance of iCa^{2+}.

Table 2. Calcium and magnesium concentrations in blood plasma of patients with acute myocardial infarction (MI) who had no MACE after MI and who had MACE after MI

	No MACE (n = 21)	MACE (n = 12)	Significance
Total Mg (mmol/l)	0.78 ± 0.10	0.80 ± 0.11	n.s.
iMg^{2+} (mmol/l)	0.55 ± 0.06	0.51 ± 0.07	p< 0.01
QMg (IMg^{2+}/total Mg)	0.72 ± 0.06	0.64 ± 0.07	p< 0.01
Bound Mg (mmol/l)	0.22 ± 0.06	0.29 ± 0.08	p< 0.05
Total Ca (mmol/l)	2.14 ± 0.29	2.07 ± 0.27	n.s.
iCa^{2+}(mmol/l)	1.17 ± 0.07	1.09 ± 0.07	p< 0.01
QCa (ICa^{2+}/total Ca)	0.56 ± 0.08	0.54 ± 0.07	n.s.
Bound Ca (mmol/l)	0.96 ± 0.27	0.98 ± 0.24	n.s.
pH	7.39 ± 0.05	7.38 ± 0.06	n.s.

MACE: major adverse cardiac events; Mg: magnesium; iMg^{2+}: ionized magnesium; Ca: calcium; iCa^{2+}: ionized calcium

Table 3. Univariate Spearman rank correlation coefficients between complications after acute myocardial infarction and possible risk factors.

Variable	Ventricular arrhythmia	CHF	Total MACE
iMg^{2+}	–0.11	–0.30*	–0.30*
Total Mg	0.15	0.12	0.07
QMg (iMg^{2+}/total Mg)	–0.35*	–0.60*	–0.52*
Bound Mg	0.34*	0.56*	0.47*
iCa^{2+}	–0.24	–0.47*	–0.41*
Total Ca	–0.07	–0.12	–0.17
QCa (iCa^{2+}/total Ca)	0.10	–0.20	–0.15
Age	0.26	0.40*	0.44*
Previous infarction	0.24	0.32*	0.29
Location of infarction	0.16	0.23	0.31*

*: $p < 0.05$; CHF: congestive heart failure; MACE: major adverse cardiac events; Mg: magnesium; iMg^{2+}: ionized magnesium; Ca: calcium; iCa^{2+}: ionized calcium

Table 4. Odds ratios of variables in multiple logistic regression analysis with total complications after acute myocardial infarction as the dependent variable.

Variable	p-value	Odds ratios
QMg	0.04	13.6 per decrease in QMg of 0.1
iCa^{2+}	0.04	8.3 per decrease of iCa^{2+} of 0.1 mmol/l
Age	0.09	1.1 per year
Previous infarction	0.26	6.9 yes/no

QMg: quotient between ionized and total magnesium; iCa^{2+}: ionized calcium

Table 5. Demographic, clinical, and laboratory characteristics as well as in-hospital treatment of both groups of patients with acute myocardial infarction

Variable	Group A (n = 23)	Group B (n = 10)	p
Age, [year]*	58.7±10.7	66.8±12.8	0.07
Gender, n, M/F	18/5	10/0	0.33
Previous infarction, %	26	70	0.05
History of angina, %	35	40	0.83
Cardiovascular risk factors			
Hypertension, %	60	50	0.64
Hyperlipidemia, %	52	50	0.94
Smoking, %	39	30	0.69
Diabetes mellitus, %	26	30	1
Peak creatine kinase level, [U/l]*	515±497	706±499	0.36
Location of infarction			
Anterior, %	35	70	0.12
Inferior-lateral, %	44	30	0.55
In-hospital treatment			
Systemic thrombolysis, %	52	50	0.94
Intracoronary thrombolysis, %	26	30	0.88
Primary coronary intervention, %	13	10	0.91
None of above, %	9	10	0.97

Group A: QMg ≥ 0.65; group B: QMg < 0.65. *Values are mean ± SD

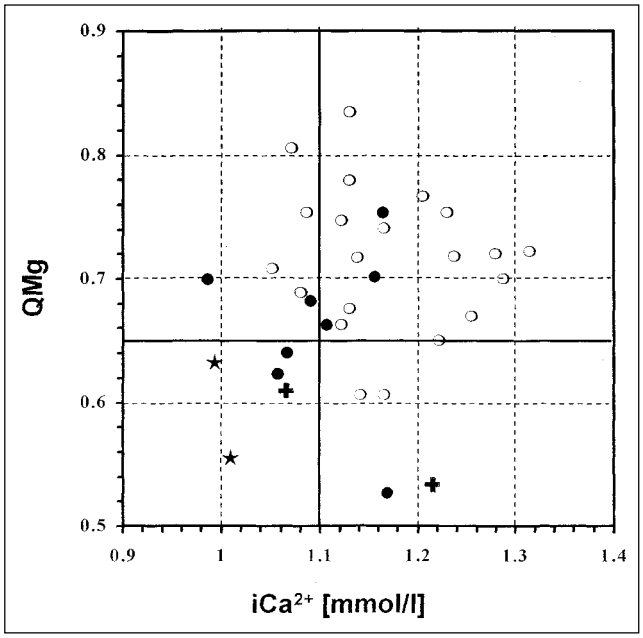

Figure 1. Relationship between the quotient of ionized and total plasma magnesium (QMg), ionized calcium values (iCa^{2+}) and the frequency of major adverse cardiac events after acute myocardial infarction. Subjects included in the square defined by QMg < 0.65 and iCa^{2+} < 1.1 mmol/l had the highest complication rate. ❍ = no complications; ● = ventricular arrhythmia and/or congestive heart failure; ★ = cardiopulmonary resuscitation; ✚ = death

For further investigation of the effect of decreased QMg, the total group was divided into 2 groups based on QMg (group A: QMg ≥ 0.65, group B: QMg < 0.65). Demographic, clinical and laboratory characteristics of the patients in both subgroups are shown in Table 5. There were no significant differences between both groups regarding age, gender, cardiovascular risk factors, peak concentration of creatine kinase and in-hospital treatment. MACE developed significantly more often in group B, resulting in higher numbers of cardiopulmonary resuscitation (20 % *vs.* 0 %) and cardiac mortality (20 % *vs.* 0 %). Ventricular arrhythmia was also found more often in group B (20 % *vs.* 0 %) whereas profound hypotension was the only complication seen in group A (26 %). Considering all adverse events, the overall complication rate was substantially higher in subgroup B:

7 out of 10 patients (70 %) with MACE and for QMg ≥ 0.65 (group A) 5 out of 23 patients (22 %). The incidence of MACE was significantly higher in group B ($p < 0.01$). Low iCa^{2+} was a predictor for MACE as well. In the group with $iCa^{2+} < 1.1$ mmol/l, 7 out of 11 patients (64 %) developed MACE as compared to 5 out of 22 patients (23 %) in the group with $iCa^{2+} \geq 1.1$ mmol/l ($p < 0.05$). The dependency of MACE upon QMg and iCa^{2+} is shown in Figure 1. The incidence of MACE, especially for ventricular fibrillation and death, is substantially higher for QMg < 0.65 and for $iCa^{2+} < 1.1$ mmol/l

Discussion

Our findings demonstrate that iMg^{2+}, the quotient between ionized and total serum magnesium QMg and iCa^{2+} may be parameters for predicting complications after acute MI. Measurement and calculation of these parameters is relatively simple and it provides the basis for an individual risk stratification after infarction. The measurement of iCa^{2+} is valuable for identifying patients whose risk of developing severe congestive heart failure might be increased if they received a magnesium supplementation.

Comparison with other studies

It is well known that magnesium is the only physiologic calcium antagonist and it modulates the transmembrane shift of the calcium ion [24, 25]. Magnesium has several cardioprotective effects, including vasodilatation [26], the reduction of platelet aggregation [27], the stabilization of cell membranes [28], reduced release of thromboxane A_2 [29] and the protection of myocardial cells from catecholamine-induced myocardial necrosis [30]. Experimental data have shown magnesium to reduce infarction size [31–33], to decrease the incidence of arrhythmia after acute MI [34], to minimize reperfusion injury [35] and to reduce stunning of the myocardium [36]. Therefore, multiple clinical trials in the setting of acute MI have been initialized to confirm the hypothesis that i.v. magnesium may have a beneficial effect in this group of patients. Whereas a number of smaller studies proved magnesium to have a positive effect on mortality [2, 37, 38], the largest investigation on 58,050 patients, the ISIS-4 study, had a nonsignificant excess in mortality in the magnesium-treated group [3]. Magnesium supplementation in the setting of an acute MI is, therefore, a matter of ongoing controversy.

In the magnesium treatment trials, neither iMg^{2+} nor iCa^{2+} were determined before treatment, but magnesium was administered to all patients of the treatment group. We determined the baseline plasma magnesium and calcium levels in patients with acute MI in order to find suitable parameters to predict the risk of complication rate.

This study represents the first investigation of ionized magnesium and calcium after acute MI for the prediction of the clinical outcome. Several studies have demonstrated iMg^{2+} to be an accurate parameter for assessing magnesium status [34–36]. In this investigation iCa^{2+} and the quotient between ionized and total magnesium turned out to be predictive in forecasting the development of complications after acute MI.

The logistic regression analysis with both ionized and total magnesium resulted in significant negative and positive respectively correlations to MACE. Since the elimination of one of the two parameters reduced the correlation of the other one to MACE below significance we introduced QMg and the difference of total magnesium and iMg^{2+} (bound magnesium) and found the closest correlation between QMg and MACE. Since lactate and total protein, especially albumin, may bind iMg^{2+} in plasma, this could effect iMg^{2+} and QMg. To test whether increases of protein and/or lactate could explain an increase of bound magnesium with a parallel decrease of iMg^{2+}, we compared bound magnesium and bound calcium as well as pH in the patients with and without MACE. If binding of divalent electrolytes to protein would have caused the decrease of QMg, the bound fractions of magnesium and calcium were to be expected to have changed in parallel in the two groups. A change in lactate, on the other hand, would have resulted in pH changes between both groups. However, there were no differences in bound calcium and in pH. The significant group difference of bound magnesium, therefore, must have been caused by another mechanism.

In a previous paper [19] we described a significant circadian variation of iMg^{2+} without a significant alteration of total magnesium. There was a significant negative correlation between iMg^{2+} and free fatty acids, indicating that iMg^{2+} is reduced during lipolysis, which can be explained by magnesium uptake into adipocytes. In the presented study the decrease of iMg^{2+} was correlated to an increase of bound magnesium, the mechanism of which is not yet understood as well as the finding that bound calcium was not increased parallel to bound magnesium.

According to our hypothesis we assume that the individual change in iMg^{2+} after an acute MI is closest correlated to the clinical outcome. For the precise determination of MI induced changes in iMg^{2+}, a pre-MI value of iMg^{2+} would be necessary. Since this is not available, total magnesium may be a suitable approximation of a pre-MI magnesium value. During acute MI, catecholamines are released in excess leading to lipolysis and a reduction of iMg^{2+} by an uptake of magnesium by adipocytes [39]. Total plasma magnesium on the other hand remains nearly unchanged during the early hours of infarction [40]. Thus, total plasma magnesium may be used as a substitute for a pre-MI indicator of the magnesium status. Multiple regression analysis with iMg^{2+} and total magnesium and the above mentioned co-variables led to nearly identical results as the analysis using QMg as the only magnesium parameter. In accordance to our hypothesis, low QMg turned out to be highly predictive of an adverse outcome in the present study. This may represent a new parameter in the assessment of risk after acute MI, whereas total magnesium alone did not predict hospital outcome of patients with acute MI [13].

The release of catecholamines is a normal reaction to acute stress and causes a liberation of magnesium, and therefore increases the iMg^{2+} [9]. Thus, in patients with a balanced magnesium status, QMg is expected to be high. Due to long-term magnesium losses, caused by chronic stress i.e. chronic noise exposure [41] and suboptimal magnesium intake,

stress-induced magnesium liberation is reduced [9]. In these patients a decrease in iMg^{2+} and QMg during an acute MI is expected. In addition, a decrease in iMg^{2+} leads to increased release of catecholamines and thus increases the risk of a *circulus vitiosus* [9, 10]. This may result in an increased risk of acute MI [41] and potential complications after infarction, especially of ventricular fibrillation as well as increased vasoconstriction of arteries [42, 43] including coronary arteries [26]. This may lead to an increased risk of congestive heart failure, while decreased iCa^{2+} may increase this risk by a pathological low calcium influx into myofibrilles. While the vasoconstriction can be counteracted by magnesium supplementation this would worsen a reduced calcium influx.

Limitations of the study

Since the number of patients involved in this study is small, the results can only be regarded as preliminary and have to be tested in a larger group of patients. Even so, the results of this study are significant for QMg and for iCa^{2+} in predicting complications after MI.

Clinical implications

Based on the results of this study, ionized magnesium and calcium should be measured in patients with an acute MI at admission to evaluate the risk for an adverse outcome. Only patients with low QMg and normal iCa^{2+} should be supplemented with magnesium infusions. Further studies are needed to verify whether the supplementation of magnesium in the subgroup of patients with a low QMg improves clinical outcome.

Acknowledgements

We are indebted to Dr. W. Babisch for assistance in the statistical analysis and to Prof. Dr. T. Günther for contributing helpful suggestions concerning biochemical mechanisms.

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