The Value of P Dispersion on Predicting Atrial Fibrillation After Coronary Artery Bypass Surgery: Effect of Magnesium on P Dispersion

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Background: AF is a frequent arrhythmia complicating CABG, and it is well known that dispersion and prolongation of P wave increases the risk of AF. The aim of this study was to investigate the effect of magnesium (Mg) treatment on P-wave duration and dispersion in patients undergoing CABG.

Method: The study included 148 consecutive patients (33 women, 115 men; mean age 62.1 ± 7.0 years) undergoing CABG who were randomly allocated to two groups. Group A consisted of 93 patients to whom 1.5 g daily MgSO_4 infusion was applied the day before surgery, just after operation, and 4 days following surgery, and group B consisted of 55 control patients. From the preoperative and postoperative fourth day, 12-lead ECG recordings, duration of the P waves, and P-wave dispersions were calculated.

Results: There were no differences between the two groups with regard to age, sex, and blood Mg level. Comparison of the baseline and day 4 ECG measurements showed no difference as far as heart rates, duration of PQ, and QRS intervals were concerned. AF developed in 2 (2%) cases in group A and in 20 (36%) cases in group B ($P < 0.001$). There was no difference between the two groups when average basal P max, P min, P dispersion, and day 4 P min values were compared. In group A, fourth day P max (94.3 ± 11.8 vs 101.0 ± 13.2 ms; $P = 0.0025$) and P dispersion (38.2 ± 9.2 vs 44.9 ± 10.9 ms; $P = 0.0002$) were significantly lower as compared to group B. Comparing the patients who developed AF, and who did not, no difference was detected with regard to baseline P max, P min, P dispersion, and day 4 P min. Day 4 P max (95.1 ± 11.8 vs 106.4 ± 14.0 ms, $P = 0.0015$) and P dispersion (38.9 ± 8.8 vs 50.7 ± 13.0 ms, $P = 0.001$) of patients who developed AF were significantly higher. Baseline Mg levels were similar in patients who developed AF, and who did not, but the day 4 Mg level was significantly lower in AF group (2.0 ± 0.23 vs 2.15 ± 0.26 mg/dL, $P < 0.001$).

Conclusion: Perioperative Mg treatment reduces P dispersion and the risk of developing AF in patients undergoing CABG.

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Atrial fibrillation (AF) occurs in a variety of settings and is generally associated with an increased risk of morbid consequences and even mortality. Identification of the risk groups for AF would have clinical importance. One group in whom the risk is well defined is those patients undergoing cardiac surgery. In this group, the incidence of AF is as high as 40%, and AF may be associated with he-

modynamic instability, thromboembolus, and prolonged hospitalization.¹ AF is common after cardiac surgery, and generally occurs within the first week after surgery.^{2,3}

Abnormalities in conduction time and excitability found in patients with a prolonged P-wave duration can predispose to the initiation of AF.⁴ The prolongation of P-wave duration is an accepted

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indicator of an interatrial conduction disturbance that can occur independent of an increase in atrial size. Consequently, prolonged P-wave duration is commonly used for the prediction of AF, idiopathic or not.^{5,6} P dispersion is a widely used valuable index that could separate patients with idiopathic AF from healthy subjects and may be used to predict the development of AF.⁷

Recent studies have demonstrated that prophylactic administration of magnesium (Mg) sulfate decreased the incidence⁸⁻¹⁰ and severity¹¹ of AF after coronary artery bypass grafting (CABG). Despite clinical relevance of Mg infusion, there is not an adequate explanation for how Mg infusion decreases the incidence of postoperative AF. The authors would like to show the effect of MgSO₄ infusion on P duration and P dispersion, and its relation with AF complication in patients undergoing CABG.

MATERIAL AND METHODS

Patients

This study was designed as a prospective, randomized, and controlled trial and included 148 consecutive patients (33 women, 115 men; mean age 62.1 ± 7.0 years) who had elective, isolated, and first time CABG over a 14-month period. Excluded from the study were patients having CABG over this time with AF or with history of AF, valvular heart disease, diabetes mellitus, chronic renal disease, thyroid disorders, chronic obstructive pulmonary disease, cardiomyopathy, congenital heart disease, congestive heart failure, pericarditis, pulmonary embolism, preexcitation syndromes, sick sinus syndrome, complete bundle branch block, atrioventricular block, and patients receiving antiarrhythmic drugs, digoxin, and beta-blocking agents. All of the subjects gave their written, informed consent, and the study was approved by the institutional review board.

Protocol

The patients were randomly allocated to two groups. Group A consisted of 93 patients to whom 1.5 g/day MgSO₄ infusion in 100 mL 0.9 NaCl solution (25 mL per hour) were applied the day before surgery, just after operation, and once daily for 4 days following surgery. Group B consisted of 55 control patients to whom 100 mL 0.9 NaCl solution (25 mL per hour) were applied at the same

time points. Mg level was measured before the treatment and daily for the postoperative 4 days. In addition to Mg measurement, potassium, sodium, chlorine and calcium concentrations were measured daily. Potassium was administered as required to maintain the concentration of potassium ≥ 4 mmol/L. All interventional procedures directed to maintain normal tissue perfusion as indicated by normal urine output, absence of metabolic acidosis, and normal lactate level. In addition to potassium and calcium measurements obtained during operation and in the intensive care unit, serum Mg, calcium, and potassium concentrations were drawn the day before surgery (before Mg or placebo infusion), 12 hours after termination of cardiopulmonary bypass, and each morning for the first 4 postoperative days. A blood gas analysis was also performed at the latter time points and oxygen saturation obtained by pulse oxymeter was recorded every 4 hours until discharge. The reference range for serum Mg in our laboratory is 1.58–2.55 mg/dL.

Data Acquisition

Standard 12-lead surface electrocardiograms (ECGs) were obtained the day before operation, just after operation, and once daily for 4 postoperative days from all patients in the supine position. During the ECG recording all participants were breathing freely but not allowed to speak. All standard 12-lead ECGs were obtained at a paper speed of 50 mm/s and 10 mm/mV. When comparing the ECG parameters, preoperative (first recording) and day 4 (last recording) ECG recordings were analyzed for comparison. The P-wave duration was calculated in all 12 leads of the surface ECG that were simultaneously recorded. The measurements of the P-wave duration were performed manually by two of the investigators without knowledge of the patient's clinical status and a magnifying lens (10-fold magnification) for defining the ECG deflections. This method has also been used by other investigators.¹²⁻¹⁴ The onset of the P wave was defined as the junction between the isoelectric line and the beginning of P-wave deflection and the offset of the P wave as the junction between the end of the P-wave deflection and the isoelectric line. The maximum P-wave duration (P maxi) in any of the 12 ECG leads was calculated and used as a marker of atrial conduction time. The difference between the maximum P-wave duration and the

minimum P-wave duration (P min) was also calculated from the 12-lead ECG. This difference, which was defined as P-wave dispersion (P dispersion), was used as a marker of the nonuniform anisotropic inhomogeneous atrial conduction. The maximum durations of the QRS complex and of the PQ segment were also calculated in all patients.

The patients were continuously monitored during their stay in the intensive care unit (ICU) using bedside monitors (Siemens, Erlangen, Germany) that are alarm triggered. After discharge from the ICU, trained nurses performed clinical observation every hour. All patients were monitored routinely with an alarm triggered 7-lead telemetry system (Siemens infinity telemetry system) until postoperative day 4 under the close attention of a monitor technician. The lower and upper alarm limits for the heart rate were 50 and 90 beats/min, respectively. When there is a question of AF on clinical grounds or by telemetry, a 12-lead ECG was obtained. All ECGs were analyzed by a cardiologist who was blinded to the study. AF was defined as the absence of consistent P waves before each QRS complex, irregular QRS complexes, and appearance of f waves.

Anesthetic Technique

The premedication used was midazolam, and the anesthesia consist of a combination of fentanyl, midazolam, and pancuronium. After tracheal intubation, mechanical ventilation was started with oxygen and nitrogen, and anesthesia was maintained with midazolam and pancuronium infusion and inhaled sevoflurane.

Operative Technique

The amount of the priming solution was kept below 1500 mL and 0.5 mg/kg furosemide was used after induction to avoid excessive hemodilution. Cardiopulmonary bypass was established by cannulation of the ascending aorta and the right atrium (double stage, single cannula), moderate hemodilution (hematocrit, 22%–25%), and moderate systemic hypothermia (32°C). Myocardial viability was preserved with topical hypothermia and cold hyperkalemic crystalloid cardioplegia (Plegisol, Abbott, Chicago, IL, USA), containing 32 mEq Mg administered intermittently into the aortic root and through saphenous grafts after each distal anastomosis. The distal anastomoses were constructed during a single period of total aortic occlusion, and

the paroxysmal anastomoses were constructed with a partial clamping of the aorta. Repeated doses of the diclofenac sodium was used for postoperative analgesia. If there was no contraindication, the patients were extubated within 6 hours after surgery. In patients with radial artery grafts, nitroglycerine infusion was started routinely after termination of cardiopulmonary bypass and carried on in the ICU, which was then changed to oral therapy for 6 months postoperatively. Short-acting nifedipine as a single dose was used for hypertension.

Statistical Analysis

Patients and in hospital characteristics were reported as mean $\pm$ SD. Demographic and clinical variables, and AF incidence were analyzed using the chi-square test and Fisher's exact for categorical variables and paired and unpaired *t*-test for continuous variables. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software 10.0 version (SPSS Inc, Chicago, IL, USA). Variables were considered significant at *P* values < 0.05.

RESULTS

There were no differences between groups A and B with regard to age and patient sex. Comparison of the baseline and day 4 ECG measurements showed no difference as far as heart rates, duration of PQ, and QRS intervals were concerned. Clinical, laboratory, and ECG parameters of all the study patients (group A and group B) are summarized in Tables 1–3, respectively.

AF developed in 2 (2%) cases in group A and in 20 (36%) cases in group B (*P* < 0.001). One of the two patients (50%) in Group A and 18 (90%) of 20 patients in Group B had sustained AF that required therapy. All of these patients were treated with amiodarone and converted to sinus rhythm, whereas in the remaining three patients, AF terminated spontaneously before discharge. None of the patients needed electrical cardioversion.

There were no differences between the two groups when average basal P max, P min, P dispersion, and day 4 P min values were compared. Comparing groups A and B, day 4 P max (*P* < 0.01) and P dispersion (*P* < 0.001) were significantly lower in group A (Fig. 1).

Table 1. Comparison of Clinical and Laboratory Parameters of Groups A and B

	Group A	Group B	P
n	93	55	
Age (years)	62.5 ± 7.0	61.3 ± 7.0	NS
Female/male (n)	21/93	12/43	NS
Baseline heart rate (/min)	74.2 ± 9.3	71.2 ± 9.5	NS
Fourth day heart rate (/min)	74.7 ± 9.9	73.6 ± 9.5	NS
Baseline QRS (ms)	84.5 ± 14.1	87.5 ± 14.1	NS
Fourth day QRS (ms)	84.4 ± 13.7	86.5 ± 14.0	NS
Baseline PQ (ms)	167.3 ± 17.0	171.5 ± 18.1	NS
Fourth day PQ (ms)	166.6 ± 15.5	170.4 ± 17.7	NS
Baseline P max (ms)	102.6 ± 14.7	104.5 ± 15.0	NS
Fourth day P max (ms)	94.3 ± 11.8	101.0 ± 13.2	0.0025
Baseline P min (ms)	54.0 ± 8.9	54.4 ± 9.1	NS
Fourth day P min (ms)	56.1 ± 9.0	56.1 ± 8.7	NS
Baseline P dispersion (ms)	48.5 ± 13.9	50.0 ± 13.7	NS
Fourth day P dispersion (ms)	38.2 ± 9.2	44.9 ± 10.9	0.0002
Baseline magnesium mg/dL	2.04 ± 0.24	2.07 ± 0.20	NS
Fourth day magnesium mg/dL	2.21 ± 0.28	1.99 ± 0.14	<0.001
Postoperative AF (+)	2 (2%)	20 (36%)	<0.001

Comparing the patients who developed AF, and who did not, no difference was detected with regard to baseline P max, P min, P dispersion, and day 4 P min. Day 4 P maxi durations were 95.1 ± 11.8 ms AF(-) group vs 106.4 ± 14.0 ms AF(+) group; $P < 0.01$, and P dispersions were 38.9 ± 8.8 ms AF(-) group vs 50.7 ± 13.0 ms AF(+) group; $P < 0.01$ (Fig. 2).

Baseline Mg levels were similar in patients who developed AF, and who did not, but the day 4 Mg

level was significantly lower in the AF group (2.0 ± 0.23 vs 2.15 ± 0.26 mg/dL; $P < 0.001$). There was no statistical differences between the two groups at any time with regard to serum potassium and calcium concentrations, blood gas parameters, and oxygen saturation.

Nineteen (20%) patients in group A, and 12 (22%) patients in group B received metoprolol ($P = NS$) as required, and 8 (9%) patients in group A, and 4 (7%) patients in group B received nifedipine ($P =$

Table 2. Comparison of Patients With and Without Atrial Fibrillation in Group A

	Group A		P
	Atrial Fibrillation (+)	Atrial Fibrillation (-)	
n	2	91	
Age (years)	66.5 ± 17.7	62.4 ± 6.8	NS
Female/male (n)	0/2	21/70	NS
Baseline heart rate (/min)	70.0 ± 7.1	74.3 ± 9.3	NS
Fourth day heart rate (/min)	73.5 ± 4.9	74.7 ± 10.0	NS
Baseline QRS (ms)	82.5 ± 3.5	84.6 ± 14.3	NS
Fourth day QRS (ms)	82.5 ± 3.5	84.4 ± 13.9	NS
Baseline PQ (ms)	162.5 ± 24.7	167.4 ± 17.0	NS
Fourth day PQ (ms)	157.5 ± 24.7	166.8 ± 15.4	NS
Baseline P max (ms)	127.5 ± 3.5	102.0 ± 14.4	0.016
Fourth day P max (ms)	110.0 ± 14.1	94.0 ± 11.6	NS
Baseline P min (ms)	55.0 ± 0.0	54.0 ± 9.0	NS
Fourth day P min (ms)	57.5 ± 3.5	56.1 ± 9.1	NS
Baseline P dispersion (ms)	72.5 ± 3.5	48.0 ± 13.5	0.020
Fourth day P dispersion (ms)	52.5 ± 10.6	37.9 ± 9.0	NS
Baseline magnesium mg/dL	2.05 ± 0.07	2.04 ± 0.24	NS
Fourth day magnesium mg/dL	2.50 ± 0.14	2.20 ± 0.28	NS

Table 3. Comparison of Patients With and Without Atrial Fibrillation in Group B

	Group B		P
	Atrial Fibrillation (+)	Atrial Fibrillation (-)	
n	20	35	
Age (years)	61.4 ± 6.9	61.3 ± 7.0	NS
Female/male (n)	4/16	8/27	NS
Baseline heart rate (/min)	70.5 ± 8.9	71.7 ± 9.9	NS
Fourth day heart rate (/min)	73.4 ± 9.9	73.7 ± 9.5	NS
Baseline QRS (ms)	85.8 ± 13.4	88.4 ± 14.6	NS
Fourth day QRS (ms)	84.5 ± 13.2	87.7 ± 14.5	NS
Baseline PQ (ms)	168.3 ± 21.5	173.3 ± 15.9	NS
Fourth day PQ (ms)	168.3 ± 20.7	171.6 ± 15.9	NS
Baseline P max (ms)	112.8 ± 15.7	99.9 ± 12.6	0.003
Fourth day P max (ms)	106.0 ± 14.3	98.1 ± 11.8	0.044
Baseline P min (ms)	52.3 ± 6.8	55.6 ± 10.1	NS
Fourth day P min (ms)	55.5 ± 7.51	56.4 ± 9.6	NS
Baseline P dispersion (ms)	60.0 ± 16.0	44.3 ± 8.0	0.0004
Fourth day P dispersion (ms)	50.5 ± 13.5	41.7 ± 7.8	0.013
Baseline magnesium mg/dL	2.02 ± 0.16	2.10 ± 0.21	NS
Fourth day magnesium mg/dL	1.96 ± 0.16	2.01 ± 0.13	NS

NS) as required for hypertension and tachycardia in the postoperative period.

DISCUSSION

In spite of the major advances in cardiac surgery, there has not been a reduction in the incidence of postoperative AF. Rather, such advances may have contributed to an increase in the incidence of AF.¹⁵ It is well known that current surgical patients are significantly older and sicker than their counter-

parts who need percutaneous coronary revascularization, and such patients experience an increased mortality.¹⁶

This study confirms that (1) the high incidence of postoperative AF (36%) in patients undergoing CABG appears in other studies, (2) a significant decrease in the incidence of AF may be achieved in patients who receive Mg infusion during the pre- and postoperative period, (3) P-wave dispersion is significantly higher in patients undergoing CABG

Figure 1. P maximum and P dispersion values in groups A and B. Pmax-0 = baseline P maximum value; Pmax-4 = day 4 P maximum value; Pdisp-0 = baseline P dispersion value; Pdisp-4 = day 4 P dispersion value.

Figure 2. P maximum and P dispersion values in atrial fibrillation (AF) (+) and (-) groups. Pmax-0 = baseline P maximum value; Pmax-4 = day 4 P maximum value; Pdisp-0 = baseline P dispersion value; Pdisp-4 = day 4 P dispersion value.

who subsequently have AF, and (4) P-wave dispersion is significantly decreased by Mg infusion during the pre- and postoperative period. The reported incidence of AF after CABG varies widely with a reported incidence of 5%–40%.¹⁷ A meta-analysis of 24 controlled, randomized trials by Andrew et al.¹⁸ who reported a pooled proportion of supraventricular arrhythmias (fibrillation and flutter) to be 26.7% with a 95% confidence interval (CI) of 24.7 to 29.1. They attributed the variation in the reported incidence of these arrhythmias to the intensity and duration of postoperative monitoring. In the present study, a telemetric monitoring system was used the day before operation and 4 days after operation, and the AF incidence is similar when compared with previous studies.

The high frequency of hypomagnesemia after cardiac surgery is well established.^{19,20} Lower serum Mg levels and lower myocardial Mg concentrations were found to be associated with increased incidence of AF.^{19,21} It must be admitted that the correlation between serum Mg levels and clinical signs and symptoms is poor, and that normal serum Mg levels may coexist with tissue Mg deficiency. The plasma Mg level may be normal in the presence of Mg depletion. By measuring the retention of administered Mg, Manners and Nielsen²² showed that 17% of the patients undergoing cardiac surgery were Mg depleted, and there was a significant positive balance in every patient in spite of normal serum Mg levels. Serum Mg concentration, although significantly higher in group A on day 4 of the operation, was similar in the baseline measurement, and was within the physiological range in both groups in the two measurements. Terzi et al.²³ reported that perioperative Mg infusion proved capable of reducing the incidence of postoperative AF in normomagnesemic patients. Hypomagnesemia, which may be a consequence of cardiopulmonary bypass surgery, seems to be unlikely in patients undergoing off-pump procedure and noncardiac thoracic surgery. However, these procedures also have high frequency of postoperative AF.^{23,24}

The electrophysiological mechanism of postoperative AF remains unclear and is presumably multifactorial. A significant contributor may be reentry resulting from dispersion of atrial refractoriness. The transient nature of this problem when seen after cardiac surgery suggests a reversible trigger; abnormal automaticity and atrial conduction delay are possible electrophysiological substrates. These

would result in the occurrence of atrial ectopy and prolonged atrial activation with lengthening of the P wave recorded by the ECG.^{25,26} However, P-wave duration, which reflects regional delayed atrial activation, is only moderately sensitive in predicting AF after CABG.^{27,28} P-wave dispersion has also been recently advocated as a novel measurement of the heterogeneity of atrial depolarization.²⁹ Previous animal studies demonstrated that dispersion of refractoriness and anisotropic conduction are two essential elements for sustaining atrial arrhythmia,³⁰ and both have been implicated in the pathogenesis of postoperative AF. The authors sought to determine if mean P duration and P dispersion from a standard ECG could provide a simple yet effective measurement of delayed and nonuniform atrial conduction in post-CABG AF. The study patients who had no clinically prior AF history did not demonstrate an increase in baseline maximal and minimal P durations and P dispersion in the two groups. In the present study, Mg infusion caused a significant decrease in day 4 maximum P duration and P dispersion. As a result, Mg infusion decreased AF after CABG, however, when the exact mechanism of the antiarrhythmic effect of Mg was looked at in these groups of patients there is not adequate explanation for how Mg infusion decreases the incidence of postoperative AF. The mechanism by which Mg reduces myocardial irritability and tachyarrhythmias is unknown. It is unclear if Mg exerts its antiarrhythmic effect by stimulating the Na-K ATPase, by directly inhibiting the efflux of potassium from the cell, by altering cellular calcium metabolism, or if it works through some other mechanism. However, it is known that the effective refractory period was relatively more prolonged than the action potential, thus causing the membrane potential to be hyperpolarized. And Mg suppresses catecholamine-induced abnormal pacemaker activity whose mechanism is increased automaticity and reentry circuits.³¹ P-wave dispersion has also been recently advocated as a novel measurement of the heterogeneity of atrial depolarization. In the present study, the most possible mechanism on reducing the effect of AF of Mg that inhibits atrial irritability and reentrant circuits in the atrial myocardium causing a prolongation of action potential and atrial refractoriness. Although this increase in atrial refractoriness is closely related with Mg infusion, we showed that presence of AF is not well correlated with serum Mg level. So, comparing the two groups baseline serum Mg

level was similar, but the forth serum Mg level was significantly higher in the Mg group as expected. Nevertheless, comparing the patients with or without AF in groups A and B, baseline and forth serum Mg levels were not significantly different from each to other. These findings may be explained with Mg cell membrane potential, for which its influx into the cell by an active ATPase system is fast. Infused serum Mg enters the cell where Mg concentration is much more than out of the cell, thus serum examination of Mg shows it in normal limits.

Despite the fact that AF is an extremely common arrhythmia following CABG, the optimal management strategy, particularly choosing the most beneficial agent and its dosing regimen, has not been established. Although numerous studies supported that Mg therapy has been decreasing the incidence of postoperative AF as in the present study, existence of the opposite opinions are not surprising.³² It is difficult to standardize and prevent predicted postoperative AF because there are many pre- and preoperative factors predisposing postoperative AF. In addition, optimal dose and strategy of Mg infusion is still controversial. Bert et al.³² showed that the postoperative incidence of AF did not decrease in patients who received Mg 12 g given during the 4-day postoperative period. They administered a higher dose Mg than was used in the present study, and it should be certain that the serum Mg level did not correctly reflect the intracellular Mg concentration which is essentially responsible for the antiarrhythmic effect. In the present study, Mg infusion was begun preoperatively and continued for 4 postoperative days. It is known that not only hypomagnesemia but also hypermagnesemia can be harmful and cause arrhythmias.³³ Parikka et al.³³ showed that totally 70 mmol of Mg sulphate infusion on the first 2 postoperative days did not reduce the incidence of AF. But those patients who developed AF were older and more of them had prior AF episodes. In addition, their sinus rates were slower than the patients who did not develop AF.

The limitations of the present study were the absence of continuous Holter ECG monitoring and manually performed P-wave analysis from surface ECG. However, because the telemetry system was alarm triggered, the patients were continuously monitored by a monitor technician, and AF was defined as lasting longer than 10 minutes or requir-

ing therapy; it seems unlikely that episodes of AF were missed.

CONCLUSIONS

The results of the study suggest that maximal P duration and P dispersion parameters on the surface ECG are simple and valuable indexes to predict the development of AF in patients undergoing CABG postoperatively. Perioperative Mg treatment reduces P duration and P dispersion and the risk of developing AF in patients undergoing CABG.

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