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Myocardial extraction of intracellular magnesium and atrial fibrillation after coronary surgery ☆

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ABSTRACT

Background: The effects of magnesium loading on the incidence of atrial fibrillation following coronary artery bypass graft surgery (CAGB) are equivocal. None of the previous studies assessed the influence of myocardial extraction of magnesium in these settings. The current trial aims to elucidate whether the incidence of atrial fibrillation following CABG is affected by the preoperative rate of myocardial extraction of magnesium.
Methods: The ethical committee approved the study protocol. 113 patients (94 male, mean age 63 ± 11 years) planned for elective CABG surgery under normothermic cardiopulmonary bypass were prospectively included. Preoperative independent variables included preoperative treatment, electrocardiographic abnormalities, left ventricular ejection fraction estimation, left atrial size, creatinine clearance and assays of plasma and intracellular magnesium, calcium, albumin, potassium and ionized calcium, drawn preoperatively from the coronary sinus and the aortic root. The covariates – including the rate of myocardial extraction of magnesium – were entered in a logistic regression model to predict the odds of atrial fibrillation.
Results: The incidence of post operative atrial fibrillation was 16%. A rate of myocardial extraction of intracellular magnesium ≥7% increases fivefold the multivariate risk of postoperative atrial fibrillation ($p<.01$). Advanced age was also significantly associated to postoperative atrial fibrillation.
Conclusions: This study suggests that a preoperative rate of myocardial extraction of intracellular magnesium ≥7% could be a new and a potent predictive factor for postoperative atrial fibrillation.

1. Introduction

Atrial fibrillation (AF) following cardiac surgery is frequent. Its incidence can reach 33% [1,2], increasing with age [3]. In the vast majority of the cases, AF occurs 24 to 96 h postoperatively, peaking on the second day [4]. Complications associated with postoperative AF include a thromboembolic risk at the short and the middle term [5], hemodynamic disturbances, prolonged hospital stay, increased cost and increased post operative mortality. Therefore, preventing post-operative AF is justified [4].

Numerous trials dealt with the pharmacological prophylaxis of postoperative AF, including beta blockers, amiodarone and sotalol [6–11]; however, few addressed the efficacy of magnesium sulfate. Hypomagnesemia is frequent in the postoperative period and is associated with an increased risk of supraventricular arrhythmias [12] and a longer duration of mechanical ventilation. Magnesium sulfate reaches its nadir on the first post-operative day then increases steadily to its preoperative levels by the fourth postoperative day. Hemodilution and renal losses are the main mechanism underlying this phenomenon [13]. Preoperative magnesium sulfate loading seems to protect from cellular ischemia, reperfusion injury [14] myocardial infarction and supraventricular arrhythmias. The meta-analysis of Miller et al. [15] showed a reduction in the incidence of postoperative AF from 28 to 18% with magnesium sulfate. However, little is known about the patients at risk, the timing, the dosing and the administration route of magnesium sulfate. Furthermore, little is known about the relation between the myocardial extraction of magnesium and the pathophysiology of postoperative AF.

We hypothesized that the variations in the extraction of magnesium by the myocardium could explain the disparities in the reported incidences of postoperative AF among the published trials. Thus, this study aims to investigate whether the rate of myocardial

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extraction of magnesium affects the incidence of postoperative atrial fibrillation.

2. Patients and methods

2.1. Patient population

This prospective study was conducted over a period of 10 months from November 2008 to August 2009. Informed consent was obtained from all the patients.

Patients with normal preoperative sinus rhythm admitted for elective coronary artery bypass graft surgery (CABG) under cardiopulmonary bypass (CPB) were eligible for the study. The exclusion criteria were: cardiac valve surgery, an ejection fraction of less than 30%, urgent surgery, preoperative supraventricular arrhythmia, the preoperative use of antiarrhythmic drugs (except for beta blockers and calcium channel blockers), abnormal hepatic tests, preoperative atrioventricular block type II or III, and an implantable defibrillator or pacemaker. None of the patients received preoperative magnesium loading.

2.2. Study protocol

The study protocol was approved by the local institutional human investigation committee. The preoperative data of every eligible patient were assessed by a targeted history including age, gender, preoperative treatment (Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin II Receptor Blockers (ARB), beta blockers, non-dihydropyridine calcium channel blockers (CCB)), an electrocardiogram (ECG), a transthoracic echocardiography (left atrial dimensions), and a preoperative blood test with assessment of the creatinine clearance.

All the operations were done under CPB, with 2 l of crystalloid priming solution, a membrane oxygenator, a roller pump and under hemodilution (hematocrit 20% to 24%). A single right atrial cannula was used for venous drainage. Myocardial preservation was uniform for all patients and consisted of epicardial ice slush and cold (4 °C), cardioplegia solution containing 30 mmol of potassium/l infused initially into the aortic root then retrograde every 15 min via the coronary sinus. A left internal mammary artery graft was used in all patients. Proximal coronary anastomoses were done under side aortic cross-clamping. Temporary atrial and ventricular epicardial pacing wires were left in all patients. Before initiating the CPB, blood samples were drawn simultaneously from the aorta (or the radial artery) – labeled "A" – and from the coronary sinus – labeled "CS" – with assays of the plasma magnesium, intracellular Mg, total calcium, albumin, potassium and ionized calcium (Ca^{++}).

During the postoperative period, all the patients were admitted for monitoring in the CSU where they were monitored by a 5-lead, alarm-triggered, electrocardiogram scope (SMU 112 Hellige, Freiburg, Germany). Patients stayed in the CSU for 48 h then transferred to the ward, with a nurse evaluation every 4 h, including clinical symptoms (palpitations, chest pain, dyspnea, and syncope), blood pressure and heart rate. The diagnosis of the atrial fibrillation after discharge from the CSU was made by ECGs done when an irregular pulse was detected, by the nurses or the doctors, or when the patient complained of a discomfort, particularly dyspnea or palpitations. A 12-lead electrocardiogram was obtained systematically twice a day. The ECGs were analyzed by the anesthesiologists and all the modifications were noted down: postoperative ST segment deviations, new onset Q waves, repolarization abnormalities, complete left bundle blocks, fascicular blocks, ventricular and atrial arrhythmias. No other prophylactic strategy for AF was used concomitantly in this study. Beta blockers were resumed shortly to avoid beta blockers withdrawal effect. Patients were considered to have had a postoperative AF if they experienced a new onset AF defined either as an episode of AF lasting more than 5 min and detected on the monitor or as an episode of AF clinically suspected and immediately confirmed by an electrocardiogram recording.

2.3. Statistical methods

Qualitative data were reported as percentages. Shapiro–Wilk and Kolmogorov–Smirnov tests were used to assess normality of quantitative data. Quantitative data were reported as mean ± standard deviation if normal or as median with its interquantile range otherwise (Median (1st Quartile–3rd Quartile)). In univariate analysis, the chi square test, the Fischer exact test, the Mann–Whitney *U* test and the *t* test were used as appropriate. The strength of the association between the independent dichotomous variables and the outcome variable was expressed by an odds ratio along with its 95% confidence interval (95% CI). Correlation between the quantitative variables was assessed using the Pearson and Spearman bivariate correlations as appropriate. In order to minimize the influence of highly correlated variables on the stability of the multivariate model, ratio of coronary sinus to arterial levels of these variables were used in the multivariate model. A ROC curve was built to set the best threshold for dichotomizing the coronary sinus to aortic root intracellular magnesium ratio, and the area under curve was calculated. All the independent variables with a univariate p value less than .25 were included in the model. A backward stepwise logistic regression model was used. All the reported p values are 2-sided and p values less than .05 were considered significant. All computations were done using SPSS v13 statistical software (Chicago, Illinois).

3. Results

During the study period, 113 patients satisfying the inclusion/exclusion criteria were enrolled. The median age was 62 (55–72) years and 83% of the patients were male. The median ejection fraction was .60 (.55–.66) and the mean LA diameter was 37.9 ± 4.3 mm. The initial patients' characteristics are listed in Table 1. The mean coronary sinus to aorta ratio of intracellular magnesium was 0.95, giving an average rate of myocardial extraction of intracellular magnesium of

Table 1
Demographic, clinical and surgical data of the 113 patients.

Variable (unit)	Statistic
Age (years)	62 (55–72)[a]
Female gender (%)	17%[b]
Preoperative EF	60 (55–66)
EF<50%	10%
LA diameter (mm)	37.9 ± 4.5[c]
LA diameter >40 mm	26%
Hypertension (%)	88.5%
Preoperative beta blockers (%)	68%
Calcium channel blockers (%)	15%
Angiotensin II Receptor blockers (%)	17%
Angiotensin Converting Enzyme inhibitors (%)	24%
Preoperative creatinine clearance (ml.min^{-1})	82 (61.5–100)
Preoperative creatinine Clearance <60 ml.min^{-1}	20.5%
Preoperative ECG	
Bundle branch block	11.5%
Myocardial infarction	29.2%
Normal	34.5%
Repolarization abnormalities	21.2%
Fascicular block	3.5%
CPB time (min)	114 ± 29
Aortic cross clamping time (min)	64 ± 19
Number of distal anastomoses	4 (3–5)

EF: ejection fraction; LA: left atrium; ECG: electrocardiogram; CPB: cardio pulmonary bypass.

[a] Quantitative non normal data are reported as median with its interquantile range (Median (1st Quartile–3rd Quartile)).

[b] Qualitative data are reported as percentage.

[c] Quantitative normal data are reported as mean ± standard deviation.

5%. The incidence of postoperative AF was 16% in this series. AF occurred at mean 2.9 ± 1.6 postoperative days; among the patients who developed AF, 22% had more than one episode and 11% more than 2. More than 90% of the recurrent AF occurred in the 2 days following the first episode. The median postoperative hospital stay was 7 [6–8] days. As shown in Table 2, the patients who developed postoperative AF were older (68 (60–76) years vs. 61 (55–70) years, p = .02), tended to have a larger LA diameter (39.7 ± 4.5 mm vs. 37.7 ± 4.2 mm, p = .07), were more likely on preoperative ACE inhibitors (OR = 3.2 (1.1–9.2), p = .03) and had lower coronary sinus to aortic ratio of intracellular magnesium (.93 (.90–.96) vs. .95 (.93–.97), p = .03). A threshold of 0.936 on the ROC curve (Fig. 1) yielded the best cut off value for dichotomizing the coronary sinus/aortic ratio of intracellular magnesium. On the average, patients with postoperative AF were fivefold likely to have had a preoperative coronary sinus/aortic ratio of intracellular magnesium less than .936 (OR = 4.65 (1.62–13.35), p < .01).

Postoperative AF was also associated with a longer postoperative hospital stay (9 (7–13) days vs. 7 (6–7) days, p < .01). However, postoperative AF was not influenced by preoperative beta blockage, ejection fraction, creatinine clearance, diuretics, or by the coronary sinus and aortic blood levels of the ions other than the coronary sinus to aortic ratio of intracellular magnesium. No correlation was found between effective furosemide dose and the coronary sinus to aortic ratio of intracellular magnesium (p = 0.863). After the multivariate adjustment, two factors remained statistically significant (Table 3): Age (multivariate OR = 1.07 (1.01–1.13) for 1 year increment) and a coronary sinus to aortic ratio of intracellular magnesium less than .936 (multivariate OR = 5.21 (1.68–16.11)).

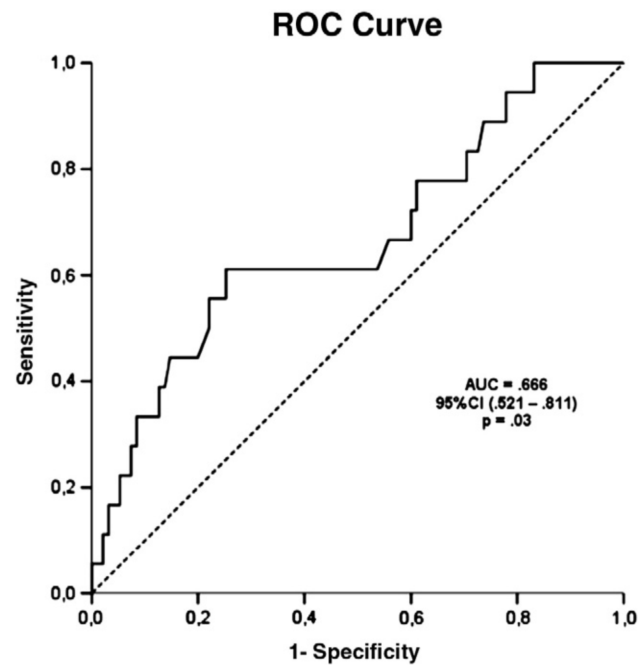

Fig. 1. ROC curve built for setting the best cut off value for dichotomizing the aortic to coronary sinus ratio of intracellular magnesium. AUC: area under curve; 95% CI: 95% confidence intervals. Diagonal segments are produced by ties.

Table 2
Univariate comparisons between the AF (n = 18) and non AF cases (n = 95).

Variable	AF group	Non AF group	p value
Dichotomous variables	OR (95% CI)	Reference	
Female gender	.57 (.12–2.7)	–	.48
ACE inhibitors	3.2 (1.1–9.2)	–	.03
ARB	.57 (.12–2.7)	–	.48
Beta blockers	.52 (.19–1.5)	–	.21
CCB	1.2 (.30–4.5)	–	.83
Ratio I Mg CS/A < .936	4.65 (1.62–13.35)	–	< .01
Continuous normal variables	Mean ± SD[a]	Mean ± SD	p value
LA diameter (mm)	39.7 ± 4.5	37.7 ± 4.2	.07
CPB time (min)	111 ± 36	115 ± 28	.46
Aortic cross clamping time (min)	61 ± 20	65 ± 18	.61
Arterial I Mg ($mmol.l^{-1}$)	2.03 ± .27	1.97 ± .17	.20
Arterial Ca ($mmol.l^{-1}$)	2.25 ± .09	2.28 ± .09	.26
Arterial Alb (g/l)	33.7 ± 4.3	34.7 ± 3.7	.34
Coronary sinus I Mg ($mmol.l^{-1}$)	1.87 ± .21	1.87 ± .17	.89
Ratio K CS/A	1.07 ± .10	1.03 ± .08	.06
Continuous non normal variables	Median (Q1–Q3)[b]	Median (Q1–Q3)	p value
Age (years)	68 (60–75)	61 (55–70)	.02
Ejection fraction	.60 (.58–.65)	.60 (.55–.66)	.66
Postoperative LOS (days)	9 (7–13)	7 (6–7)	< .01
Creatinine clearance ($ml.min^{-1}$)	80 (56–100)	84 (65–100)	.64
Number of distal anastomoses	4 (3–4)	4 (3–5)	.61
Arterial P Mg ($mmol.l^{-1}$)	.80 (.70–.90)	.80 (.80–.80)	.79
Arterial K ($mmol.l^{-1}$)	3.90 (3.80–4.20)	3.90 (3.70–4.10)	.42
Arterial Ca++ ($mmol.l^{-1}$)	1.02 (.96–1.10)	1.06 (.99–1.12)	.36
Coronary sinus Ca++ ($mmol.l^{-1}$)	1.15 (1.10–1.19)	1.16 (1.11–1.18)	.45
Coronary sinus P Mg ($mmol.l^{-1}$)	.80 (.70–.90)	.80 (.79–.80)	.79
Coronary sinus Ca ($mmol.l^{-1}$)	2.21 (2.10–2.28)	2.22 (2.12–2.29)	.82
Coronary sinus Alb (g/l)	36.0 (31.4–38.0)	36.0 (32.0–38.0)	.97
Coronary sinus K ($mmol.l^{-1}$)	4.05 (3.80–4.40)	4.00 (3.70–4.30)	.25
Ratio P Mg CS/A	1.00 (1.00–1.00)	1.00 (1.00–1.00)	.98
Ratio I Mg CS/A	.93 (.90–.96)	.95 (.93–.97)	.03
Ratio Ca CS/A	.98 (.95–0.99)	.98 (.94–1.00)	.78
Ratio Ca++ CS/A	1.08 (1.01–1.19)	1.07 (1.02–1.18)	.99

AF: atrial fibrillation; ACE: Angiotensin Converting Enzyme; ARB: Angiotensin II Receptor Blocker; P: plasmatic; I: intracellular; A: aortic; CS: coronary sinus; Mg: magnesium; Ca: total calcium; Alb: albumin; K: potassium; Ca++: ionized calcium; SD: standard deviation; OR (95% CI): odds ratio with its 95% confidence interval; LOS: length of stay.
[a] Quantitative normal data are reported as mean ± standard deviation.
[b] Quantitative non normal data are reported as median with its interquantile range (Median (1st Quartile–3rd Quartile)).

4. Discussion

To our knowledge, no previous work assessed the correlation between the rate of myocardial extraction of intracellular magnesium and the incidence of postoperative AF in patients undergoing elective CABG surgery under CPB. The incidence of postoperative AF was 16% in this series. The coronary sinus to aortic ratio of intracellular magnesium was sorted out as the most powerful predictive factor for postoperative AF, increasing its likelihood up to fivefold. Advanced age had a significant but less important effect, and the effect of the other covariates collapsed after multivariate adjustment.

Hypomagnesemia is frequent in the postoperative period, resulting mainly from hemodilution and renal losses [13]. Magnesium sulfate reaches its nadir on postoperative day 1 then catches its preoperative levels by postoperative day 4 [16]. Hypomagnesemia increases the risk of supraventricular arrhythmias [12]. However, the net effect of magnesium loading on postoperative AF incidence is equivocal: Hazelrigg et al. [17] found no effect, whereas the meta-analyses of Shiga et al. [18] and Miller et al. [15] found a significant reduction, and more recently, Cook et al. found no effect of magnesium loading in the largest randomized, placebo-controlled trial for the prevention of AF

Table 3
Final step of the multivariate backward stepwise logistic regression model.

Variable	OR (95% CI)	p value
Age (years)	1.08 (1.02–1.12)	< .03
Aortic to coronary sinus ratio of Intracellular magnesium < .936	5.21 (1.68–16.11)	< .001

OR (95% CI): odds ratio with its 95% confidence interval; Nagelkecke's R2 = .23. Hosmer–Lemeshow statistic = .86.

after CABG or cardiac valvular surgery [19]. However, none of the previous magnesium trials addressed the relation between the rate of myocardial extraction of magnesium and the pathophysiology of post operative AF, or the effect of magnesium loading on the rate of myocardial extraction of magnesium.

The main finding in this study was that the coronary sinus to aortic ratio of intracellular magnesium was lower in patients who developed postoperative AF. Dichotomizing this ratio and setting a threshold of .936 derived from the ROC curve shows a fivefold increase in postoperative AF incidence, confirmed once more upon multivariate adjustment. In other words, a preoperative myocardial extraction of intracellular magnesium higher than 7% increases the likelihood of postoperative AF by 5.

One might wonder what these findings can add up to the previous work in that field. In fact, they help reinterpret – at least partially, besides sample sizes and patient selection considerations – the controversy surrounding the results of the different magnesium trials for preventing postoperative AF; one hypothesis is that previous trials randomized patients irrespective of their intracellular magnesium CS/A ratios: [1] those trials that enrolled a significant proportion of patients with low intracellular magnesium CS/A ratios – or high extraction rates – showed significant results of magnesium loading; [2] the other trials enrolled a significant proportion of patients with high I magnesium CS/A ratios – or low extraction rates – showing no significant results of magnesium loading; [3] the negative trials could have found significant results by virtually stratifying the patients according to their intracellular magnesium CS/A ratios. However, these hypotheses hold true only if magnesium loading corrects the high cardiac extraction rate of intracellular magnesium, another hypothesis yet to be demonstrated.

Unsurprisingly, the effect of age remained significant after multivariate adjustment, confirming the constant relation between advanced age and postoperative AF [4]. Aging is associated with modifications of the cardiac structures, chambers dilation and fibrosis. However, linking these modifications to an increased propensity for postoperative AF occurrence after CABG remains elusive. Left atrial dilation is one of the most involved mechanisms in the occurrence of AF, including postoperative AF [2], but its effect was less important in the actual trial after inclusion in the multivariate model. In univariate analysis, preoperative treatment with ACE inhibitors increased the risk for postoperative AF, while this effect disappeared after multivariate adjustment. The published data concerning this issue are conflicting: systemic hypertension was a risk factor for postoperative AF in some studies [1], while preoperative treatment with ACE inhibitors and ARBs decreased this risk in other [20].

4.1. Limitations of the study

This trial has several limitations: first, the lack of continuous Holter monitoring after discharge from the CSU to the floor where the diagnosis of the atrial fibrillation was made by ECGs done when an irregular pulse was detected, usually by the nurses, the physicians, or when the patient complained of a discomfort, particularly dyspnea or palpitations. As AF occurrences can be asymptomatic, it is possible that a significant proportion of the AF burden has never been detected; therefore missing brief sequences of AF could have altered the estimation of AF incidence. Second, the threshold of .936 for intracellular magnesium CS/A ratio was not based on previous known physiologic or pathophysiologic work, but was deduced from the ROC curve resulting from the sampling distribution of the actual observed data. The intracellular magnesium CS/A ratio – as a continuous variable – was found significant, which is the main finding of this trial, but dichotomization allows building a simple decision rule without altering the initial solution. Third, some highly correlated covariates were not included in the multivariate analysis due to their detrimental effect on the model consistency and error types 1 and 2 inflation. Fourth, repeating the measures of the intracellular magnesium CS/A ratio before weaning from bypass could have added more information on this ratio's kinetics and its association with postoperative AF. Finally, the findings of this trial need an external validation before they can be extrapolated.

5. Conclusion

In this series of patients undergoing elective CABG surgery under CPB, the preoperative coronary sinus to aortic ratio of intracellular magnesium – or the rate of myocardial extraction of intracellular magnesium – was the most powerful predictive factor of postoperative AF, increasing its likelihood by fivefold. Further clinical studies are needed to validate these findings and to elucidate their role in the genesis of postoperative AF.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [21].

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