Special review

Magnesium for Atrial Fibrillation after Coronary Artery Bypass Graft Surgery: its Role in Aetiology and Prevention

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ABSTRACT

Objective: *To summarise the potential consequences of atrial fibrillation (AF) after coronary artery bypass graft surgery (CABG) and the relationship of the arrhythmia with serum magnesium concentration ([Mg]) and to review the trials of magnesium supplementation as prophylaxis against post-CABG AF.*

Data sources: *Abstracts, articles and published reviews on AF after CABG and magnesium prophylaxis.*

Summary of review: *AF after CABG occurs in 20-40% of patients. It may cause haemodynamic compromise, stroke, prolongation of hospital stay and an increased use of resources. Effective prophylaxis offers the enticing prospect of reductions in morbidity, hospital stay and resource utilisation.*

There is circumstantial evidence suggesting that hypomagnesaemia may predispose to cardiac arrhythmias. Serum [Mg] falls after CABG due to haemodilution and beta-adrenergic mediated mechanisms. Several studies have reported an association between hypomagnesaemia and post-CABG AF, but a causal relationship has not been established. Trials have demonstrated that magnesium (Mg) replacement can attenuate the perioperative fall in serum [Mg], but have failed to show efficacy of Mg therapy in AF prevention after CABG. The perioperative changes in serum [Mg] do not seem to reflect changes in intracellular magnesium, including within the atria.

Conclusions: *AF after CABG is common and a drain on resources through its association with increased morbidity and hospital stay. Previous studies investigating the relationship between serum [Mg] and AF after CABG have produced inconsistent results. The current evidence from randomised, placebo-controlled trials does not support the use of Mg therapy to prevent AF after CABG and strengthens the likelihood of any association between post-CABG AF and hypomagnesaemia being a passive one. That Mg appears ineffective as prophylaxis for postoperative AF may partly be due to limitations in trial methodology, but most probably reflects the poor correlation between serum total [Mg] and intracellular magnesium, specifically the intra-atrial magnesium content.* (**Critical Care and Resuscitation 2000; 2: 260-268**)

Key Words: Magnesium, atrial fibrillation, coronary artery bypass graft surgery

Atrial fibrillation (AF) is a common complication after coronary artery bypass graft surgery (CABG) occurring in 20-40% of patients.[1,2] It presents most frequently on the second to fourth postoperative day and

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is often paroxysmal. It remains the subject of considerable interest predominantly because the arrhythmia is associated with a number of adverse clinical and financial outcomes. Furthermore, there has been no significant decrease in its incidence over the last 30 years. This has stimulated research to identify aetiological mechanisms, predictors and preventive strategies for post-CABG AF.[3]

Hypomagnesaemia has been proposed as a cause for cardiac arrhythmias including AF after CABG. In addition, magnesium (Mg) supplementation has been used to prevent the arrhythmia. This paper will summarise the potential consequences of post-CABG AF. In addition, we will review the relationship of AF after CABG with serum magnesium concentration ([Mg]) and the trials of Mg supplementation as prophylaxis.

Adverse postoperative outcomes

Haemodynamic compromise

AF has the potential to cause haemodynamic compromise with a reduction in stroke volume and cardiac output and an increase in atrial and ventricular end-diastolic pressures.[4-9]

In animal models and clinical studies, AF caused cardiac output to fall by 18-30%.[10-12] Such haemodynamic changes are clearly undesirable in the early postoperative period, many CABG patients having limited cardiac reserve.

Postoperative stroke

AF plays a clear causative role in the aetiology of thromboembolic events.[13-15] In the non-postoperative population, the risk of stroke does not seem to differ between those with paroxysmal AF and those with chronic AF,[15,16] both predisposing to thrombus formation within the left atrium. Thus, patients who develop AF after CABG are also significantly more likely to suffer a stroke in the early postoperative period[2,17-21] (Table 1) even after accounting for other predisposing factors such as old age.[2,19]

Morbidity

AF after CABG is associated with increased morbidity, although without a clear causal relationship in most cases. In addition to neurological injury, the occurrence of AF has been independently associated with the increased need for intraoperative aortic balloon pump, as well as increased rates of postoperative pneumonia, cardiac failure, renal failure, prolonged ventilation and return to the intensive care unit.[17,20,22]

Table 1. Incidence of postoperative stroke in patients with and without AF after CABG

Study		*AF*	*Non-AF*	*P value*
Cresswell[2] 1993	n = 3983*	3.3%	1.4%	< 0.0005
Aranki[17] 1996	n =570	3.7%	1.0%	< 0.03
Taylor[18] 1987	n = 453†	7.0%	1.0%	< 0.005
Chung[19] 1995	n = 6899‡	6.6%	3.5%	0.0001
Almassi[20] 1997	n = 3855§	5.3%	2.4%	0.001

* included 71% isolated CABG; § 81% isolated CABG; † stroke and transient ischaemic attack (TIA) rate; ‡ stroke and TIA and non-cerebral embolism.

Prolongation of hospital stay and additional expenditure

Patients who develop AF have a prolonged hospital stay after CABG (Table 2).

Table 2. Duration of postoperative hospital stay in AF and non-AF patients

Study		*Postoperative hospital stay (days)*		
		AF	*Non-AF*	*P value*
Cresswell[2] 1993	n = 3983*	10.9	7.5	0.0001
Mathew[22] 1996	n = 2265†	12.8 (9)	10.2 (7)	< 0.01
Aranki[17] 1996	n =570	15.3 (10)	9.4 (7)	0.001
Borzak[24] 1998	n = 436	9.4	6.3	< 0.01
Kowey[23] 1997	n = 157	(10)	(7)	< 0.0001
Almassi[20] 1997	n = 3855§	(10)	(7)	0.001
Zaman[3] 2000	n = 326	9.2	7.3	< 0.0005
Tamis[25] 2000	n = 216	15.2	10.0	< 0.001
Rubin[26] 1987	n = 123	14.4	12.4	< 0.02
Mendes[27] 1995	n = 168	10.1	8.4	0.02
Zaman[28] 1997	n = 102	7.9	6.8	< 0.01

Open figures are means; bracketed figures are median values;
* Included 71% isolated CABG; † 90% isolated CABG; § 81% isolated CABG.

Time spent in the intensive care unit is significantly prolonged by between 13 hours and 2.3 days,[2,20,21] while total postoperative hospital stay is increased by 1.1-5.9 days in AF patients.[2,3,17,23-28] Furthermore, recent evidence confirms that the increased length of hospitalisation is attributable to the arrhythmia itself independent of other patient characteristics such as age and comorbid-ity.[24,25] The financial burden resulting from postoperat-ive AF is, therefore, considerable (Table 3).[17,22,23] One analysis of resource utilisation estimated that the addit-ional hospital charges resulting from the occurrence of AF were more than $10,000 per patient.[17]

Table 3. Additional expenditure per patient attributable to AF after CABG

Study	*Prolongation of stay (days)*	*Additional cost*
Mathew[22] 1996 n = 2265*	2.6	$ 1 616
Aranki[17] 1996 n =570	4.9	$ 10 055
Kowey[23] 1997 n = 157	(3)	($ 7 867)

Open figures are means; bracketed figures are median values
* Included 90% isolated CABG.

Adverse effects of treatment

Treatment strategies for patients with post-CABG AF include ventricular rate control, electrical or chemical cardioversion, maintenance of sinus rhythm with antiarrhythmic agents, and anticoagulation.[29-31] The anti-arrhythmic agents used to treat AF have potentially harmful side effects including hypotension, bradycardia and conduction disorders. Most are negatively inotropic. Of particular importance is their proarrhythmic potential[32-34] and patients with preexisting heart disease are at higher risk of serious ventricular arrhythmias from these drugs.[34,35] Nevertheless, the majority of patients who develop post-CABG AF receive antiarrhythmic treatment.[36-40]

Numerous strategies to prevent AF after CABG have been investigated, driven by the prospect of achieving concomitant reductions in morbidity, hospital stay and resource utilisation. A lack of consistent results in unselected patients has mitigated against adoption of a uniform prophylactic strategy.[26,41-43] Beta-blockers may be effective prophylactic agents but interpretation of the beta-blocker trials is complicated by the pro-arrhythmic effect of withdrawal of these agents in patients randomised to control.[44] The failure of effective drug therapy underlines the importance of strategies to define aetiological mechanisms and individuals vulnerable to post-CABG AF.

The relationship between hypomagnesaemia and cardiac arrhythmias

Background

A relationship between hypomagnesaemia and cardiac arrhythmias has previously been proposed.[45] Evidence to support causality comes from 1) anecdotal case reports of arrhythmias in patients who have a low serum [Mg],[46,47] 2) studies showing an association between low serum [Mg] and arrhythmias,[48,49] and 3) the suppression of arrhythmias by Mg administrat-ion.[50,51] In addition, *in vitro* and *in vivo* experiments have demonstrated that the alteration of extracellular [Mg] affects the electrophysiological properties of cardiac tissue.[52-55] Indeed, Mg is an essential cofactor of the sodium-potassium ATPase and therefore plays a central role in maintaining the cell resting membrane potential.

Most of the clinical research interest surrounding Mg has revolved around the possibility of a relationship between hypomagnesaemia and ventricular arrhythmias. The possible relationship between serum [Mg] and AF has received much less scrutiny. Specifically, the role of hypomagnesaemia in the aetiology of AF after CABG has been investigated in only a few studies. This is perhaps surprising given the common simultaneous occurrence of hypomagnesaemia and AF after CABG.

Hypomagnesaemia after CABG: occurrence and mechanisms

Patients with severe coronary artery disease have a lower mean serum [Mg] than healthy controls.[56] The reason for this is unknown but diuretic treatment for cardiac failure or hypertension and secondary hyperaldosteronism probably contribute. Thus, patients coming to CABG are at risk of hypomagnesaemia.[57]

Serum [Mg] falls further during cardiac surgery. A study of 200 patients undergoing CABG found that serum [Mg] fell from a mean preoperative level of 0.81 mmol/L to a low of 0.61 mmol/L on the first postoperative day ($p < 0.001$), prior to a gradual return to preoperative levels by the fourth day after CABG.[58] Similar findings have been replicated in other studies.[28,59-62]

One mechanism underlying this perioperative fall in serum [Mg] is haemodilution as a result of prime fluid in the extracorporeal circuit being returned to the circulation and additional intravenous fluid administration. If this were the sole explanation, however, then the concentration of other ions and proteins would be expected to decrease by a similar magnitude. Studies in this area have reported contrasting results,[58,60-65] but one study found that the proportional perioperative decrease in serum [Mg] was significantly greater at day one and day three than the proportional decrease in serum [total protein] among patients who underwent cardiopulmonary bypass (CPB).[65] It seems unlikely, therefore, that the fall in serum [Mg] is explained by haemodilution alone. An additional mechanism that has been proposed involves the stress-induced release of adrenaline causing beta-adrenergic mediated lipolysis and an increase in circulating fatty acids.[65-70] The intracellular concentration of ionised Mg subsequently drops following intracellular precipitation of insoluble Mg soaps. Transient hypomagnesaemia may result from Mg transfer from the extracellular to the intracellular space.[69,70]

Is hypomagnesaemia associated with AF after CABG?

The common simultaneous occurrence of hypomagnesaemia and cardiac arrhythmias in the

postoperative period has led investigators to consider a causal relationship between serum [Mg] and arrhythmias after CABG. In 1983, Bunton retrospectively analysed 200 patients undergoing CABG in four groups: uncomplicated, perioperative myocardial infar-ction, perioperative myocardial infarction and dysrhyth-mia, and dysrhythmia alone.[58] In all patients, serum [Mg] was lowest on the first postoperative day but there was no difference in [Mg] between the four groups. Furthermore, when each dysrhythmia was analysed individually, no difference was found between [Mg] in the 36 patients who developed AF and the rest.

In a different study of 101 patients undergoing cardiac surgery (70% CABG), 19.2% had a low serum [Mg] preoperatively compared with 71% immediately after CPB.[71] Atrial arrhythmias were significantly more common in patients who were hypomagnesaemic after CPB, but the frequency of these arrhythmias was the same when patients with low and normal [Mg] on the first postoperative day were compared. Furthermore, in a prospective study of 128 cardiac surgical patients (77% CABG) who received 24-40 mmol Mg in the perioperative period, there was no association between postoperative arrhythmias (mostly AF) and any of, pre- or postoperative serum [Mg], perioperative Mg flux, or perioperative change in [Mg].[72] Thus, the authors concluded that while Mg deficiency may play a role in the aetiology of arrhythmias, the serum total [Mg] was not a useful measurement upon which to base preventive or therapeutic measures in cardiac surgical patients. This is consistent with the findings of a case-control study which reported no significant difference in the incidence of hypomagnesaemia (20% v 25%) between 40 patients with, and 40 patients without supraventricular tachycardia after CABG.[73]

Two subsequent prospective observational studies of patients undergoing CABG have reported that the mean postoperative serum [Mg] was significantly lower in patients who developed AF. In the first study of 131 patients, mean serum [Mg] 48 hours after surgery was 0.79 mmol/L in AF patients compared with 0.83 mmol/L in non-AF patients.[74] There was a larger difference (0.62 v 0.72 mmol/L; $p < 0.001$) in the second study of 102 patients, when serum [Mg] was measured on the first postoperative day.[28] Importantly, hypomagnesaemia was an independent predictor for AF with a sensitivity of 85%, a specificity of 58% and a positive predictive accuracy of 45%.

In summary, serum [Mg] tends to fall after CABG and there are a number of possible explanations for this. Several studies have reported an association between hypomagnesaemia and post-CABG AF, but a causal relationship has not been established.

Does magnesium protect against AF after CABG? Trials of magnesium prophylaxis

That Mg has antiarrhythmic properties and hypomagnesaemia may play a role in the aetiology of AF after CABG led to studies investigating Mg supplementation to prevent the arrhythmia (table 4).[75-86]

Table 4. Summary of reviewed trials of magnesium prophylaxis for post CABG AF

Study		*Incidence of AF*		*p value*
		Mg	*Control*	
Schwieger[75] 1989	n = 200*	11%	17%	NS
England[76] 1992	n = 100†	20%	34%	0.11
Karmy-Jones[77] 1995	n = 100‡	26.1%	24.1%	0.83
Speziale[78] 2000	n = 97	4%	20%	0.05
		0%		0.04
		4%		0.05
Fanning[79] 1991	n = 99	14.3%	28%	NS
Parikka[80] 1993	n = 139	29%	26%	NS
Caspi[81] 1995	n = 98	44%	37.5%	NS
Nurozler[82] 1996	n = 50	4%	20%	0.02
Jensen[83] 1997	n = 57	34.5%	35.7%	NS
Shakerinia[84] 1996	n = 50	20%	32%	NS
Woodend[85] 1998	n = 496§			NS
Solomon86 2000	n = 167	22.4%	19.5%	0.65

NS = not significant; * Included 70% isolated CABG; † 84% CABG; ‡ 86% CABG; § A meta-analysis

In some of these trials the study populations were heterogenous, including patients undergoing valve surgery. Nevertheless, in one trial of 200 patients who underwent cardiac surgery (70% isolated CABG), serum [Mg] was measured at six-hourly intervals and patients were randomised to receive either Mg supplementation (Mg sulphate in 1 g increments) to maintain a serum [Mg] > 2 mEq/L, or control.[75] Mean [Mg] was significantly higher in the Mg group (1.8 v 1.5 mEq/L; $p < 0.05$) but there was no significant difference in the frequency of atrial arrhythmias (11% v 17%). Two further trials randomised 100 patients (of whom at least 84% underwent isolated CABG) to receive either Mg supplementation irrespective of serum [Mg], or placebo. In one trial, 2 g Mg chloride was administered over 30 minutes after the termination of cardiopulmonary bypass,[76] and in the other, 2.4 g Mg sulphate over 20 minutes at the end of cardiopulmonary bypass was given, followed by a further five doses at four-hourly intervals.[77] There was no significant reduction in the incidence of new supraventricular tachycardias (20% v 34%; $p = 0.11$ and 26.1% v 24.1%; $p = 0.83$, respectively) in either trial.

Several trials are confined to CABG patients only.

One recent study reported that Mg supplementation reduced postoperative AF.[78] Ninety seven patients undergoing CABG were divided into four groups. In group A, 25 patients had 1 g Mg sulphate added to the pump prime. In group B, 25 patients had 1 g Mg sulphate added to the pump prime plus 5 mmol/L Mg added to the cardioplegic solution. In group C, 22 patients had 5 mmol/L Mg added to the cardioplegic solution and in group D, 25 patients received placebo. Patients in groups A, B and C also received a 24 hour infusion of Mg 10 mmol/L. In all groups the serum [Mg] decreased during CPB, but it remained significant-ly below the preoperative level after CPB only in group D. AF occurred significantly less frequently in group A (1/25; $p = 0.05$), group B (0/22; $p = 0.04$) and group C (1/25; $p = 0.05$) compared with group D (5/25).

The majority of trials, however, have demonstrated no benefit from Mg therapy. In one trial of 99 patients, actively treated patients received intravenous Mg sulphate 96 mEq in the first 24 hours postoperatively followed by 24 mEq/day for the next 72 hours.[79] Seven (14.3%) patients developed AF in the Mg group compared with 14 (28%) in the placebo group, a non-significant difference. The number of episodes of AF, however, was significantly reduced (12 v 42; $p < 0.02$) by Mg.

The equivocal role of Mg supplementation is further highlighted by a study of 139 CABG patients in which Mg-treated patients received 40 mmol Mg sulphate in the first 24 hours after surgery, followed by 30 mmol over the next 24 hours.[80] Again, there was no significant difference in the incidence of AF (29% v 26%) between the Mg and placebo groups. In fact, the incidence of AF *increased* progressively among patients from the lowest to highest quartile of serum [Mg] as measured on the first postoperative day.

A further trial studied 98 patients with unstable angina undergoing CABG.[81] Myocardial protection was by blood cardioplegia which contained 32 mEq/L of Mg. Patients were randomised to receive either an additional 16 mmol of Mg sulphate during surgery followed by 32 mmol over the first 24 hours post-operatively, or placebo. Although the postoperative serum [Mg] was significantly higher in the Mg group than the placebo group, there was no significant difference in the incidence of AF (44% v 37.5%) between the two groups.

More recently, 50 CABG patients were randomised in double-blind fashion into two equal groups to receive either 100 mEq Mg sulphate over the first postoperative day followed by 25 mEq from the second to fifth day (plus 16 mmol/L Mg in the cardioplegia) or placebo (and Mg-free cardioplegia).[82] One patient (4%) in the Mg group developed AF compared with five (20%) in the placebo group ($p = 0.02$). Two further randomised trials of similar size, however, found no reduction in the incidence of AF in Mg-treated patients (34.5% v 35.7% and 20% v 32%, respectively).[83,84]

A meta-analysis of four randomised, placebo-controlled trials of Mg prophylaxis in 496 patients undergoing CABG revealed an odds ratio of 0.75 for the development of AF in the actively treated patients compared with controls, but the difference between groups was not significant (confidence interval 0.48-1.18).[85]

A recent report has also shown that Mg in combination with propranolol offered no additional protective effect against AF after elective first CABG compared with propranolol alone.[86] Indeed, combinat-ion therapy was associated with a significantly increased incidence of hypotension (43.5% v 24.4%; $p = 0.01$).

In reviewing these studies, it is important to note several limitations. The study populations were frequently small and non-uniform. The post-surgical course of serum [Mg] may differ after valve surgery compared with CABG and may be dependent upon the method of myocardial protection employed. Further-more, the influence of Mg replacement may differ between these groups. Arrhythmia definition and monitoring were not standardised and Mg supplement-ation regimens were also different. Nevertheless, despite demonstrating that Mg replacement can attenuate the perioperative fall in serum [Mg], these studies have failed to show efficacy of Mg in atrial arrhythmia prevention after CABG and strengthen the likelihood of the association between post-CABG AF and hypomagnesaemia being a passive one.

Why does magnesium replacement not protect against AF after CABG?

Normally, Mg exists in blood in three forms: 1) bound to proteins, 2) complexed to anions like bicarbonate, phosphate, sulphate, etc., and 3) free, biologically active, ionised Mg. About two thirds of the serum Mg is in the ionised form, but total serum [Mg] does not accurately reflect serum ionised [Mg].[87,88] There is also clear evidence that serum total [Mg] does not correlate with intracellular Mg content, either in mononuclear blood cells,[89] red blood cells, lymphocytes,[90] skeletal muscle[70] or cardiac muscle.[91] Of particular note, right atrial appendage [Mg], serum and mononuclear cell [Mg] were measured in 100 patients undergoing cardiac surgery.[91] Right atrial appendage [Mg] prior to the institution of CPB was significantly lower (103 v 111 microg/g wet-weight; $p = 0.009$) in the 47 patients who developed arrhythmias (supravent-ricular tachycardia, ventricular tachycardia or ventric-ular fibrillation requiring treatment) compared with the

52 who did not. Right atrial appendage [Mg] did not correlate with mononuclear cell [Mg] or serum [Mg] and the investigators concluded that serum [Mg] did not predict myocardial [Mg]. In a different study of 18 CABG patients, a decrease in mean serum [Mg] of 17.3% on initiation of CPB was accompanied by a fall in right atrial myocardial Mg content of 13% (3.87 to 3.36 microg/g of wet tissue; $p < 0.05$), but there was no significant change in skeletal muscle Mg content.[92] By contrast, there was no significant decrease in right atrial Mg content after CPB in a further study of 31 patients who underwent CABG.[93] Moreover, both right atrial and skeletal muscle Mg contents were similar before and after CPB in AF and non-AF patients. Thus, while serum total [Mg] and ionised [Mg] fall perioperatively, this does not seem to reflect changes in intracellular [Mg], including in the atria. This is a possible explanation for the failure of Mg supplementation to prevent AF after CABG.

Conclusion

AF occurs in about one third of patients after CABG. In most cases, it is a benign, self-limiting condition, but there is clear evidence that the arrhythmia is associated, probably in a causal manner, with adverse clinical and financial outcomes. Numerous preventive strategies have been reported, but a lack of consistent results means that there is no generally accepted prophylactic strategy. For these reasons, AF after CABG, specifically the question of effective prophy-laxis, continues to generate considerable interest.

Hypomagnesaemia is common in patients with severe coronary artery disease and serum [Mg] falls further after CABG. Previous studies investigating the relationship between serum [Mg] and AF after CABG have produced inconsistent results. Magnesium is an attractive agent for prophylaxis against post-CABG AF because it possesses neither negative inotropic properties nor carries the risk of proarrhythmia. The current evidence from randomised, placebo-controlled trials, however, does not support the use of Mg to prevent AF after CABG. This may partly be due to limitations in trial methodology, but most probably reflects the poor correlation between serum total [Mg] and intracellular [Mg], specifically the intra-atrial Mg content.

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