Magnesium deficiency may be an important determinant of ventricular ectopy in digitalised patients with chronic atrial fibrillation

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Digitalised patients with chronic atrial fibrillation (AF) have a high prevalence of ventricular premature beats (VPB); magnesium deficiency may be a contributory factor. We have used a magnesium loading-test to examine the relationship between ventricular ectopy and magnesium status in 14 digitalised patients with chronic AF. Among seven patients with infrequent VPB ($< 250 \text{ 24 h}^{-1}$; mean 107 24 h^{-1}) mean magnesium retention was 10.1% and four subjects retained no significant quantities of magnesium, indicating magnesium repletion. Among the remaining seven patients, mean magnesium retention was significantly higher (33.1%, $P < 0.02$) and all patients retained 20% or more of the load given. There was an overall relationship between Mg retention and numbers of VPB ($r_s = 0.54$; $P < 0.05$). Magnesium deficiency may be determinant of ventricular ectopy in digitalised patients with chronic AF.

Keywords magnesium digoxin atrial fibrillation

Introduction

In previous studies we have noted a high prevalence of ventricular ectopy among digitalised patients with chronic atrial fibrillation (AF): 18/48 of these patients consistently had more than 1,000 ventricular premature beats (VPB)/24 h (Currie *et al.*, 1989; Lewis *et al.*, 1988, 1989a,b). It is possible that this may, in part, be a consequence of magnesium (Mg) deficiency as hypomagnesaemia is one of many factors which may predispose to arrhythmia (Chadda *et al.*, 1973; Dyckner, 1980; Dyckner & Wester, 1979), particularly during digoxin therapy (Seller *et al.*, 1970).

Up to 20% of patients with chronic AF have hypomagnesaemia (Martin & Milligan, 1987; Martin *et al.*, 1988; Whang *et al.*, 1985), although serum Mg concentrations are not a reliable guide to Mg status (Elin, 1987). Others have reported that increased retention of Mg following intravenous loading with 30 mmol of magnesium chloride over 12 h is a better predictor of Mg deficiency (Caddell, 1985; Jones *et al.*, 1969; Rasmussen *et al.*, 1988). We have therefore used this test to examine the relationship between ventricular ectopy and Mg status in digitalised patients with chronic AF.

Method

Fifteen patients (mean age 61; range 58–74 years: seven females) were entered into the study. All had chronic AF of at least 1 year's duration. In eight patients the AF was thought to be secondary to ischaemic heart disease while the remaining seven had echocardiographic evidence of rheumatic heart disease. All patients were taking digoxin on a long-term basis and nine were also taking diuretics ('Frusene': 2, 'Dyazide': 3, 'Moduretic': 1, bumetamide: 1, frusemide: 1, bendrofluazide: 1). Doses of digoxin were adjusted, where necessary, to achieve serum digoxin concentrations of between 1.3 and 2.6 nmol l⁻¹ when measured 6–8 h after dosing.

At their first visit, patients underwent venous blood sampling (without a tourniquet) for measurement of urea, electrolytes, magnesium and digoxin concentrations; 24 h urine collection for measurement of Mg and creatinine excretion, and 24 h ambulatory ECG monitoring using Marquette 2-channel recorders. At their second visit, patients were admitted to a research ward where an infusion of 30 mmol of magnesium chloride in 50 ml of 0.9% saline was given over 12 h via an infusion pump. All urine passed for 24 h following the start of the infusion

Table 1 Relationships between ventricular ectopy and electrolyte status in 14 patients with atrial fibrillation, divided into two main groups according to prevalence of ventricular premature beats (VPB)
(a) *Infrequent VPB (< 250 24 h⁻¹)*

VPB 24 h ⁻¹	Serum Mg (mmol l ⁻¹)	Serum K (mmol l ⁻¹)	Basal urinary Mg excretion (mmol 24 h ⁻¹)	Mg retention (%)	Diuretic
132	0.95	4.1	1.4	0	'Dyazide'
18	0.82	4.3	2.2	24	'Moduretic'
11	0.91	4.5	5.4	0	—
173	0.84	4.3	1.7	20	—
1	0.92	3.8	4.2	23	'Bendrofluazide'
195	0.83	4.0	4.4	4	—
218	0.80	4.4	3.1	0	—
Mean					
107	0.87	4.2	3.2	10.1	

(b) *Frequent VPB (> 250 24 h⁻¹)*

VPB 24 h ⁻¹	Serum Mg (mmol l ⁻¹)	Serum K (mmol l ⁻¹)	Basal urinary Mg excretion (mmol 24 h ⁻¹)	Mg retention (%)	Diuretic
1828	0.94	4.5	2.6	20	'Frusene'
326	0.94	4.5	3.9	33	'Frusene'
1807	1.03	5.7	4.2	31	'Bumetamide'
431	0.89	4.4	2.5	51	—
365	0.83	3.9	3.2	43	'Dyazide'
2025	0.92	3.4	1.8	25	—
2520	0.82	3.9	6.2	29	'Dyazide'
Mean					
1329	0.91	4.3	3.5	33.1*	

* $P < 0.02$ for differences between patients with frequent and infrequent VPB

was collected. Continuous ECG monitoring was undertaken throughout the course of the infusion and the heart rate and blood pressure were recorded at hourly intervals. At the third visit, 7–14 days after the Mg infusion, further 24 h ambulatory ECG monitoring was undertaken and repeat measurements were made of serum Mg and electrolyte concentrations, and urinary and Mg creatinine excretion. Twenty-four hour urinary creatinine excretion was compared between the three samples from each patient to ensure that urine collection was complete.

Serum digoxin concentrations were measured using a radio-immunoassay technique and Mg concentrations in serum and urine were measured using atomic absorption. Magnesium retention was calculated from 24 h urinary Mg excretion during and after Mg loading, expressed as a percentage of the total load given (30 mmol). Twenty-four hour ambulatory ECG recordings were examined for numbers of VPBs: results of automated counts were, whenever possible, substantiated by inspection of print-outs of abnormal rhythm to differentiate between true ectopy and aberrancy (Rapeport & Schamroth, 1985). Results were examined using nonparametric statistical methods: namely the Mann-Whitney U test and the Spearman rank correlation.

Results

One patient withdrew from the study prior to Mg loading because of intercurrent illness. Among the remaining 14 patients, none experienced any adverse effects

during the Mg infusion apart from mild cutaneous flushing and, in one individual, a transient headache. There was a small fall in mean arterial blood pressure (average 8 mm Hg) during the Mg infusion.

Examination of baseline 24 h ambulatory ECG recordings showed that all subjects had VPB, ranging in frequency from 1 to 2520 (mean 718) 24 h⁻¹. The 14 patients were divided into two equal groups according to prevalence of ventricular ectopy; seven patients had fewer than 250 VPB 24 h⁻¹, a figure generally considered to be clinically unimportant, the mean for this group being 107 VPB 24 h⁻¹. The other seven patients had more than 300 VPB 24 h⁻¹; the mean for this group was 1329 VPB 24 h⁻¹. These two groups were comparable in terms of age and sex distribution. Diuretic usage was greater among those with frequent VPB (5 vs 3).

Magnesium retention varied widely and significantly between the two groups. In those patients with infrequent VPB, mean Mg retention was 10.1% and 4/7 patients retained no significant amount of the Mg load (Table 1). In contrast, among the seven patients with frequent VPB, mean Mg retention was significantly higher (33.1%: $P < 0.02$) and all seven subjects retained 20% or more of the i.v. load (Table 1). Serum magnesium concentrations and basal urinary Mg excretion were similar in the two groups (Table 1). There was a weak overall relationship between Mg retention and the prevalence of ventricular ectopy ($r_s = 0.54$; $P < 0.05$). There were no significant changes in serum Mg concentrations or basal urinary Mg excretion before and after Mg loading and numbers of VPB were similar (718 vs 808 VPB 24 h⁻¹).

Discussion

The present study demonstrates a significant relationship between the prevalence of ventricular ectopy and retention of Mg following i.v. loading, suggesting that magnesium deficiency may be associated with ventricular arrhythmia. Magnesium retention differed widely between the two groups and 4/7 patients with infrequent VPB retained virtually no Mg following i.v. loading suggesting that they were Mg replete. In contrast, among the patients with frequent VPB, all seven subjects retained 20% or more of the i.v. Mg load, indicating probable Mg deficiency. However, it should be noted that, among the seven patients with frequent ectopics, those with 300–400 VPB 24 h^{-1} tended to retain more Mg than those with $> 1,000\text{ VPB }24\text{ h}^{-1}$. Our division of the 14 patients into two equal groups may be somewhat arbitrary, and the finding of a significant if weak independent overall relationship between Mg retention and VPB for all subjects may be considered a more acceptable analysis of the data. Because of the numbers involved, detailed subgroup analysis is not possible with our data but there is no evidence to suggest that Mg deficiency was any less prevalent among those six patients who were taking a potassium sparing diuretic, despite evidence to suggest that such agents also promote Mg retention by the kidney (Ryan *et al.*, 1981). The dose of Mg given would be insufficient to correct moderate

degrees of Mg deficiency and we cannot, therefore, draw any conclusions from this study about the effects of the Mg on ventricular ectopy. In previous studies, however, we have shown a decrease in VPB during supplementation with oral magnesium glycerophosphate (Lewis *et al.*, 1989b).

The importance of Mg deficiency is debatable and others have concluded that Mg depletion, of the magnitude commonly associated with diuretic usage, is unlikely to be of relevance to most patients (Ramsay, 1986). However, there are reasons to suppose that Mg deficiency may be a clinically important entity in some patients with underlying heart disease. Atrial fibrillation is predominantly a disease of old age (Camm *et al.*, 1980) and studies have shown that dietary intake of Mg may be deficient in elderly people (McConway *et al.*, 1981). The long-term ingestion of diuretics and digoxin, both of which increase urinary Mg excretion (Kupfer & Kosovsky, 1965; Nanji, 1983), may compound problems brought about by a low dietary intake of Mg and others have reported a relatively high prevalence of hypomagnesaemia among digitalised patients with chronic AF.

Our results suggest that Mg deficiency, as diagnosed using a Mg loading test, may be a determinant of ventricular ectopy in digitalised patients with chronic AF. The possibility that this may predispose to more serious forms of ventricular arrhythmia cannot be excluded.

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