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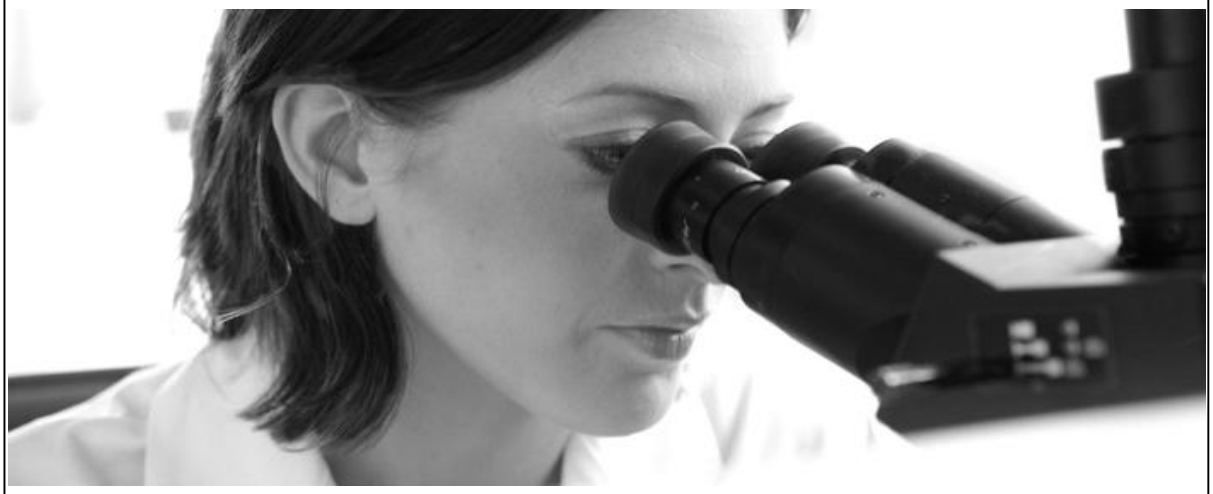

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RESEARCH ARTICLE

PLASMA MAGNESIUM CONCENTRATIONSIN PAROXYSMAL ATRIAL FIBRILLATION

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ABSTRACT

Introduction: Magnesium is an essential element in maintaining myocardial transmembrane potential. Little is known about its contribution to atrial fibrillation (AF) appearance. **Purpose:** To study plasma magnesium concentrations in paroxysmal AF (PAF) with a view to their possible role in the clinical presentation of the disease. **Materials and methods:** 33 patients (17 men, 16 women; mean age 60.03±1.93 years) and 33 controls with no history of AF (17 men, 16 women; mean age 59.27±1.72 years) were examined. In patients, magnesium was tested three times: on entering the ward, twenty-four hours and twenty-eight days after sinus rhythm restoration. In controls the indicator was determined once. **Results:** Upon admission there was no significant difference in magnesium concentrations between patients and controls (1.21±0.02 vs 1.17±0.03 mmol/L, p=0.33). Twenty-four hours and twenty-eight days after the arrhythmia discontinuation, still there was no difference (1.23±0.04 vs 1.17±0.03mmol/L, p=0.29; 1.21±0.02 vs 1.17±0.02 mmol/L, p=0.23, respectively). **Conclision:** This is the first clinical trial for plasma magnesium levels in PAF. No changes in the microelement values were measured during and after the arrhythmia. This fact was reason to believe that magnesium has no relation to AF clinical course and its values could not be used in monitoring the disease.

INTRODUCTION

Magnesium is a divalent cation that performs essential cell functions. It is the second most abundant intracellular and the fourth most common cation in the entire human body (Fawcett *et al*, 1999). It is located primarily in tissues with enhanced metabolic activity such as the brain, heart, liver and kidneys. Only about 1% of its total content is in the extracellular space. Its significance is often underestimated by forgetting the fact that it performs more than 300 different physiological functions (Parikh *et al*, 2012). In practice, magnesium is related to the catalytic function of enzymes requiring a nucleotide co-factor (Schmitz *et al*, 2004). Changes in its concentrations are associated with oxidative stress, pro-inflammatory state, endothelial dysfunction, platelet aggregation, insulin resistance and others (Cunha, 2012).

Magnesium has also antiarrhythmic properties. They were described for the first time in 1935 by Zwillinger (Zwillinger, 1935). He presents eight patients with atrial or ventricular fibrillation as a result of digitalis toxicity, which restore sinus rhythm after administration of the element in the form of sulphate salts. Today it is well known that magnesium affects a number of phases of the cardiac action potential. Its electrophysiological properties, exhibited at cellular level, are less known than those of potassium, although the functions of both cations are closely linked (Rude, 1989). Both extracellular and cytosolic magnesium are related to the regulation of the duration of action potential, cell excitability and contractility (Geiger, 2012). It participates in the action potential of the myocardium primarily by influencing the activity of the calcium and potassium channels (Piotrovski, 2004). Magnesium is a physiological inhibitor of the voltage-dependent L-type calcium channels in atrial cardiomyocytes during phase 2 of the action potential (Faghighi *et al*, 2008). At the same time it reduces calcium release from the sarcoplasmic reticulum. Moreover, magnesium mediates potassium influx during phase 4 (Guiet-Bara *et al*, 2007).

Summarizing the data, we can say that the electrophysiological effects of the cation on the atrial myocardium are quite complex. Magnesium increases the conduction time and refractoriness of cardiomyocytes and thus reduces the number of re-entry outbreaks of excitement in the atria. Furthermore, it can inhibit the early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) occurring during repolarization. A series of studies have shown that a major substrate for initiation, retention and recurrence of atrial fibrillation (AF) is the electrical remodeling of the atria (Nattel *et al*, 2008; Shiroshita-Takeshita *et al*, 2005). It occurs in the first hours of clinical manifestation of the rhythm disorder (Issac *et al*, 2007). It is characterized by shortening of the duration of action potential and refractory period in either ways: reduction of inward L-type calcium current and enhancement of outward

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potassium current that can promote and sustain re-entry rotors. In addition, alterations in calcium handling are observed that promote diastolic calcium release and ectopic activity as DADs (Nattel *et al*, 2008; Iwasaki *et al*, 2011).

The above-mentioned facts gave a serious reason for conducting this study whose objective was to investigate the plasma concentrations of magnesium in patients with paroxysmal atrial fibrillation (PAF) with a view to their possible role in the development and clinical manifestation of the disease.

MATERIALS AND METHODS

Study design

We screened only patients with PAF and time of the arrhythmia occurring <48 hours prior to examination. All could clearly define the beginning of the rhythm disorder as a sudden onset of "heartbeat" continuing to the time of hospitalization. The diagnosis was accepted only after it was objectified by ECG. In the absence of contraindications mentioned elsewhere (Bellandi *et al*, 1995; Bianconi *et al*, 1998) an acute drug attempt with propafenonewas performed to restore sinus rhythm. After the discontinuation of the rhythm disorder patients were monitored for a minimum of 24 hours and subsequently discharged from hospital. They were followed up for 28 days (4 weeks) after restoration of sinus rhythm, during which two control examinations were carried out - on the seventh and twenty-eighth day after regularization of the rhythm.

Blood samples were taken three times –upon hospitalization of the patients (baseline values of magnesium plasma concentrations), 24 hours and 28 days after regularization of the rhythm.

A control group was formed whose participants had no history or ECG evidence of AF. Their blood was tested once.

Study participants

The study was conducted in the Intensive Cardiology Department of First Cardiology Clinic at the University Hospital "St. Marina "- Varna for the period October 2010 – May 2012 after approval by the Research Ethics Committee (№35/29.10.2010) at the same hospital and in accordance with the Declaration of Helsinki (WHO, 2008). The participants were included in the study after previously signing the informed consent for participation.

33 patients were selected sequentially (17 men, 16 women; mean age 60.03±1.93 years) with drug restored and detained until the end of the study sinus rhythm.

Exclusion criteria included a number of diseases

1. Cardiovascular diseases: coronary artery disease; heart failure; implanted devices to treat rhythm conduction disorders; inflammatory and congenital heart diseases; moderate or severe acquired valvular defects; cardiomyopathies;
2. Other diseases: renal, pulmonary or hepatic failure; diseases of the central nervous system; inflammatory and/or infectious diseases in the past three months; neoplastic or autoimmune diseases; diseases of the endocrine system (with the exception of type 2 diabetes mellitus, non-insulin dependent);
3. Hormone replacement therapy, pregnancy, systemic administration of analgesics including NSAIDs; obesity with BMI>35;
4. Inability to determine the onset of arrhythmia; persistent rhythm disorder after the 24-hour regimen of propafenone; restoration of sinus rhythm by electrical cardioversion; AF recurrence by the end of the study (*exclusion criteria for patients*).

The same exclusion criteria were applied to form the control group. The selection of study participants (patients and controls) aimed to equalize to the maximum the factors affecting plasma magnesium concentrations in both groups. 33 controls were selected for the study (17 men, 16 women; mean age 59.27±1.72 years).

Sample collection and storage. Analytical methodology

Magnesium concentrations were examined in plasma obtained from peripheral venous blood. Blood samples were collected in heparin vacutainer (VACUETTE/4.0 ml/Li Hep) and immediately centrifuged at 2000g for 10 min. The resulting plasma was immediately pipetted, frozen at –20°C and kept under the same conditions for up to 3 months.

In conducting the study re-freezing of samples was not allowed.

Analytical methodology

Plasma magnesium concentrations were determined spectrophoto metrically. The reagent we used was by Beckman Coulter, USA in full compliance with the manufacturer guidelines. The basis of the methodology is the reaction of magnesium ions with xylolblue, during which a colored complex stable compound with a pink-red color is formed and is subjected to photometry at 600 nm. The staining intensity is proportional to the concentration of magnesium in the sample measured in mmol/L.

Regimen of propafenone

Restoration of sinus rhythm was achieved after administration of the drug propafenone. The drug was administered in the prescribed for it scheme with a total duration of 24 hours (Bellandi *et al*, 1995; Bianconi *et al*, 1998). After restoration of sinus rhythm until the end of the study (28 days after restoration of rhythm) all patients received a maintenance dose of p.o. propafenone of 150 mg three times daily.

Statistical analysis

We used descriptive statistics to calculated the means, standard deviations, relative shares and central tendency (Mo = mode).

The testing of the hypothesis for equality of means and indicators for relative share was done by Student's t-test. A two-sided t-test was used in our study for independent (unpaired) samples at a level of significance of p=0.05. Values of p <0.05 were used to confirm the hypothesis that the difference between the means was statistically significant.

RESULTS

Characteristics of study subjects

The patient and control group did not differ statistically in number of participants, average age and gender structure (p>0.05) (Table 1). Also the frequency of accompanying diseases, dyslipidemia and their ongoing treatment (until hospitalization) as well as BMI values were approximately the same for both groups (p>0.05) (Table 2). Statistical analysis showed that the mean duration of AF until hospitalization was 8.64±1.03 hours. All patients were hospitalized between the second and the twenty-fourth hour of the beginning of the episode.

Table 1 Demographic and clinical characteristics of the participants

	Patients with PAF	Control group	P values
Number of participants in the group	33	33	p=1
Mean age (years)	60.03±1.93	59.27±1.72	p=0.77
Men/Women	17/16	17/16	p=1

Table 2 Drug treatment of accompanying diseases and BMI

	Patients with PAF	Control group	P values
Accompanying diseases			
Hypertension	21 (63.64%)	24 (73.73%)	p=0.38
Diabetes mellitus type 2	1 (3.03%)	1 (3.03%)	p=1
Dyslipidemia	3 (9.09%)	1 (3.03%)	p=0.30
Medicaments for Hypertension and Dyslipidemia			
Beta blockers	8 (24.24%)	10 (30.30%)	p=0.58
ACE inhibitors	10 (30.30%)	7 (21.21%)	p=0.40
Sartans	5 (15.15%)	6 (18.18%)	p=0.74
Statins	2 (6.06%)	1 (3.03%)	p=0.55
Metformin	1 (3.03%)	1 (3.03%)	p=1
BMI (kg/m2)	23.86±2.84	23.98±2.75	p=0.86

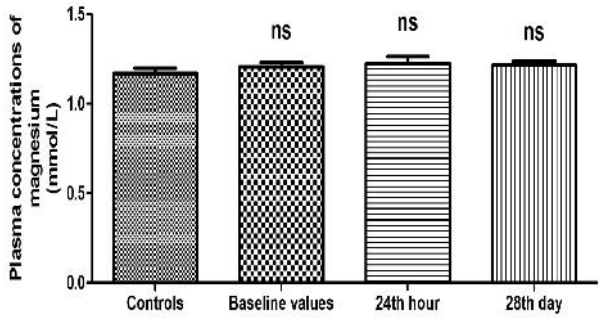

Figure 1 Magnesium plasma concentrations (mmol/L) of patients with PAF and controls. (baseline values - immediately after hospitalization of the patient, 24th hour - 24 hours after discontinuation of the arrhythmia; 28th day - 28 days after discontinuation of the arrhythmia; ns - statistically insignificant difference).

Plasma magnesium concentrations

Upon entering the ward there was no statistically significant difference in plasma concentrations of magnesium, measured in patients and controls (1.21±0.02 vs 1.17±0.03 mmol/L, p=0.33) (Figure 1). Twenty-four hours and twenty-eight days after the discontinuation of the rhythm disorder there were also no differences (1.23±0.04 vs 1.17±0.03 mmol/L, p=0.29; 1.21±0.02 vs 1.17±0.02 mmol/L, p=0.23, respectively).

DISCUSSION

AF is increasingly perceived in medical circles as the "new non-communicable epidemic" given its ever-increasing incidence (Lip *et al*, 2007). The low efficiency of present treatment is a prerequisite for new studies in search of the pathogenetic mechanisms of the disease. In this sense electrolyte disturbances, and in particular blood levels of magnesium in AF, represent research interest. The problem is particularly relevant in post CABG AF, given the ion imbalance that normally occurs in the course of the operation. Studies up to date indicate that the occurrence of the arrhythmia correlates with serum levels of the element. Its preoperative and early postoperative intravenous application reduces the incidence of AF (Bakhsh *et al*, 2009; Chelazzi *et al*, 2011; Najafi *et al*, 20079). Other studies did not establish such an effect (Klinger *et al*, 2015; Svagzdiene *et al*, 2009). According to Sahin *et al*. (2010) there was no statistically significant difference in blood levels of magnesium in patients with and without occurrence of postoperative AF, and it is therefore logical for the treatment with magnesium salts to be result less (Sahin *et al*, 2010). The study of Frick *et al*. (2000) confirms this statement. It showed no reduced recurrence of postoperative AF after intravenous administration of magnesium.

Changes in blood levels of the element are also researched in other forms of AF, unrelated to cardiac operations. For example, De Carlli *et al*. (1986) measured decreased levels of magnesium in patients with symptomatic persistent or permanent AF. Their results indicate that magnesium deficiency is observed in approximately 20% of patients.
Single studies research the importance of magnesium for the clinical course of the PAF. Chiladakis *et al*. (2001) found that magnesium sulfate favorably affects rate control and seems to promote the conversion of long lasting episodes of PAF to sinus rhythm. Brodsky *et al*. (1994) present similar results. However, there is no data on plasma levels of the element in patients with PAF.

Our study is the first to examine this issue. The results showed no statistically significant variation in plasma magnesium concentrations in patients with PAF (p>0.05) (Figure 1). There are no changes both during the clinical manifestation of the arrhythmia as well as twenty-eight days after the restoration of sinus rhythm. In analyzing the data we should emphasize the fact that the concentrations of magnesium were not determined only once. Their tracking in time gives grounds to believe that the results presented by us are not accidental laboratory findings and reflect the actual status of the element in plasma. The threefold examination provides the opportunity to establish that the rhythm disorder is not associated with changes in plasma magnesium concentrations both during the clinical appearances as well as four weeks later. There wereno dynamics in the plasma levels of the element andtherefore the

values of the indicator could not be used in monitoring and predicting the clinical course of the disease. It should be also noted that the initial values are determined in the early hours of the disease. The rhythm disorder episodes are of short duration, which significantly limits the accumulation of changes. Therefore we cannot comment and accordingly transfer our results to other types of AF, such as persistent and permanent AF, where the time of the onset of the arrhythmia prior to examination is much longer.

In analyzing the results, it is also appropriate to note that the plasma levels of the element do not reflect most adequately its content in the tissues (Khan *et al*, 2013; Piotrawski *et al*, 2004). Although the correlation between blood and intracellular levels is relatively good, it is possible, although rare,to observe non-compliancies(Khan *et al*, 2013;). In this sense, the absenceof changes in plasma could not be easily regarded as an equivalent to the absence of changes in the atrial myocardium. This could explain why intravenous application of magnesium sulphate in some studies has a positive effect on the discontinuation of AF paroxysms.

CONCLUSION

This is the first clinical trial that examines plasma magnesium levels in PAF. . No changes in the microelement values were measured during and after the arrhythmia. This fact was reason to believe that magnesium has no relation to AF clinical course and its values could not be used in monitoring the disease.

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