

REVIEW PAPERS

**THE ROLE OF MAGNESIUM IN CARDIAC
ARRHYTHMIAS**

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Abstract

Magnesium plays an essential role in many fundamental biological reactions, as it is involved in more than 300 metabolic reactions. Deficiency of magnesium may result in many disorders, including cardiac arrhythmias. As intravenous magnesium has a high therapeutic to toxic ratio and a minimal negative inotropic effect, it has long been used in treatment and prevention of cardiac arrhythmias. Several studies have shown the beneficial effect of intravenous infusion of Mg during an attack of supraventricular tachycardia, indicating that the effectiveness of magnesium depends on the type of tachycardia. Magnesium has also an advantageous effect in the case of atrial fibrillation, considered a criterion of the effectiveness of atrial fibrillation acute treatment at the ventricular rate $\leq 100 \text{ min}^{-1}$.

As intravenous magnesium seems to be useful in prevention and treatment of various cardiac arrhythmias, it is a common component of a complex antiarrhythmic therapy.

Key words: magnesium, arrhythmia, supraventricular tachycardia, atrial fibrillation.

ROLA MAGNEZU W ARYTMIACH SERCA

Abstrakt

Celem pracy była ocena magnezu w arytmiach serca. Magnez odgrywa istotną rolę w wielu podstawowych procesach biologicznych, ponieważ bierze udział w ponad 300 reakcjach metabolicznych. Niedobór magnezu może spowodować wiele zaburzeń, w tym zaburzenia rytmu serca. Ze względu na wysoki stosunek efektywności terapeutycznej do toksyczności, magnez od lat jest stosowany w leczeniu i zapobieganiu arytmii serca. Liczne badania wykazały korzystny wpływ dożylniej infuzji magnezu podczas ataku częstoskurczu nadkomorowego, wskazując jednocześnie, że skuteczność magnezu zależy od rodzaju częstoskurczu. Magnez ma również korzystny wpływ w przypadku migotania przedsionków, jeżeli za kryterium skuteczności przyjąć uzyskanie rytmu komorowego $\leq 100 \text{ min}^{-1}$.

Ze względu na korzystny wpływ magnezu w zapobieganiu i leczeniu różnych zaburzeń rytmu serca, stanowi on częsty element złożonej terapii przeciwarytmicznej.

Słowa kluczowe: magnez, arytmia, częstoskurcz nadkomorowy, migotanie przedsionków.

INTRODUCTION

Magnesium plays an essential role in many fundamental biological processes, as it is involved in more than 300 metabolic reactions. It participates in many enzymatic reactions, binding to a substrate or directly to an enzyme, thus altering its structure. Moreover, magnesium ions play a crucial role in the functioning of many ion channels, including cardiac Mg^{2+} -sensitive K^+ channels, which normally allow K^+ to pass more readily inward than outward. As magnesium regulates the outward K^+ movement, potassium is transported equally well in both directions when Mg^{2+} is absent. Therefore, magnesium deficiency may lead to a reduced amount of intracellular K^+ , which disturbs the resting membrane potential of the heart muscle cells and results in cardiac arrhythmias (RUDE, SHILS 2006).

Cardiac conduction system

Cardiac arrhythmia is caused by a wrong rate or rhythm of the heartbeat (tachycardia: too fast heartbeat; bradycardia: too slow heartbeat), which are controlled by the cardiac conduction system (Figure 1). Each heartbeat begins with an electrical signal generated by the sinoatrial node (SAN), which is the dominant pacemaker site in the heart, located in the lateral right atrium (RA). Electrical impulses are conducted from the SAN to the rest of the RA and left atrium (LA) via specialized interatrial connections including the Bachmann's bundle. The electrical signal then moves downwards to a group of cells called the atrioventricular node (AVN), normally the only electrical connection between the atrium and ventricle. Electrical impulses transmitted through the AVN are conducted rapidly through the His bundle, which branches into a right and a left bundle. The terminal Purkinje fibers connect with the ends of the bundle branches, forming an

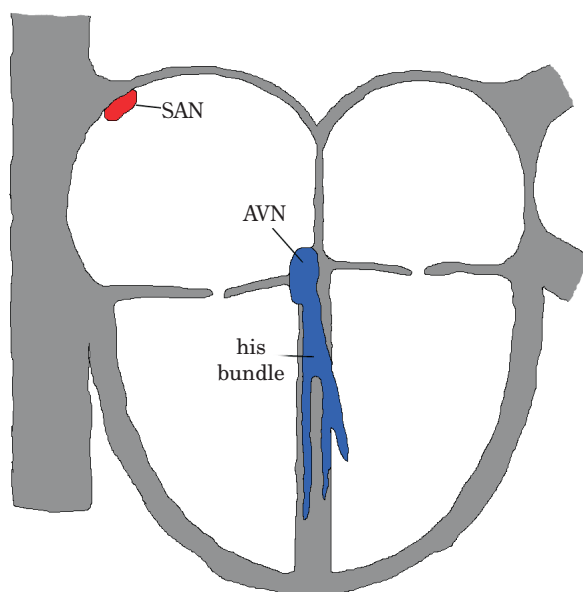


Fig. 1. Key elements of heart conduction system: SAN – sinoatrial node, AVN – atrioventricular node (based on: BENDER et al. 2011, modified)

interweaving network on the endocardial surface so that a cardiac impulse is transmitted almost simultaneously to cardiac muscle cells of both ventricles. Any malfunction during any part of this process can cause arrhythmia <http://www.nhlbi.nih.gov/health/health-topics/topics/arr/> (BENDER et al. 2011).

Antiarrhythmic function of magnesium – the mechanism

Mechanisms of the antiarrhythmic function of magnesium are only partially known. As magnesium is a cofactor of the membrane Na-K pump, its deficiency can reduce the pump's activity, leading to partial depolarization and changes in the activity of many potential-dependent membrane channels (ANGUS, ANGUS 2001). Extracellular Mg can also penetrate into another ion channel, reducing the ion movement rate through the channel. Such an action on the L-type calcium channel makes magnesium a physiological calcium antagonist (HESS et al. 1986, WU, LIPSIVS 1990). Magnesium infusion has also been reported to increase significantly the sinus node recovery time (with correction of sinus node recovery time), atrioventricular node (AVN) conduction time during a sinus rhythm, atrial paced cycle length at which an AV node Wenckebach block occurred, AV node relative refractory period, functional refractory period and effective refractory period (DiCARLO et al. 1986). As mentioned earlier, magnesium can also regulate the functioning of cardiac K^+ ion channels (RUDE, SHILS 2006).

Magnesium in various arrhythmias

Intravenous magnesium has a high therapeutic to toxic ratio and a minimal negative inotropic effect and has been used for years in treatment and prevention of cardiac arrhythmias. It is commonly believed that magnesium deficiency is an important pathogenetic factor responsible for supraventricular and ventricular arrhythmias. This dependence, however, is a complex one because magnesium is an intracellular ion and a systemic deficiency may coincide with normal magnesium blood levels.

Magnesium produces various electrophysiological effects, hence it has been reported to be efficient in prevention and treatment of various cardiac arrhythmias. Several studies have shown that intravenous infusion of Mg during an attack of supraventricular tachycardia (Figure 2) effectively pro-



Fig. 2. Electrocardiogram of a patient with supraventricular tachycardia

longs the RR interval, slows down the atrioventricular (AV) conduction and restores the sinus rhythm (WESLEY et al. 1981, STILES et al. 2007, SAGER et al. 1990, VISKEN et al. 1992). Invasive electrophysiological studies carried out on patients with paroxysmal supraventricular tachycardia indicate that the effectiveness of magnesium depends on the type of tachycardia. The study by STILES et al. (2007) revealed that intravenous (iv) magnesium extended the tachycardiac cycle to a greater extent in patients with the dual AVN conduction than those without it. This effect was also associated with a longer AH interval in patients with the dual AVN physiology than in ones without it. Besides, the presence of dual AVN conduction was more frequently associated with a reversion to the sinus rhythm. Research has also shown that an attack of recurrent supraventricular tachycardia in AVN could be interrupted by iv magnesium, while recurrent atrioventricular tachycardia was resistant to such therapy (STILES et al. 2007). Considering the above results, it is unsurprising that magnesium is commonly used in cases of supraventricular tachycardia. However, comparison of magnesium to adenosine or verapamil reveals that antiarrhythmic drugs, especially adenosine, are more effective than magnesium in relieving supraventricular tachycardia.

Atrial fibrillation (Figure 3) is a serious clinical problem, especially in elderly patients, because it is often associated with a high risk of thromboembolic complications and increased mortality. Successful electrical cardioversion restoring the sinus rhythm only partially solves the problem due to the high probability of the recurrence of arrhythmia (Vos 2004). As hypomagnesemia is diagnosed in 20-50% of patients with paroxysmal atrial

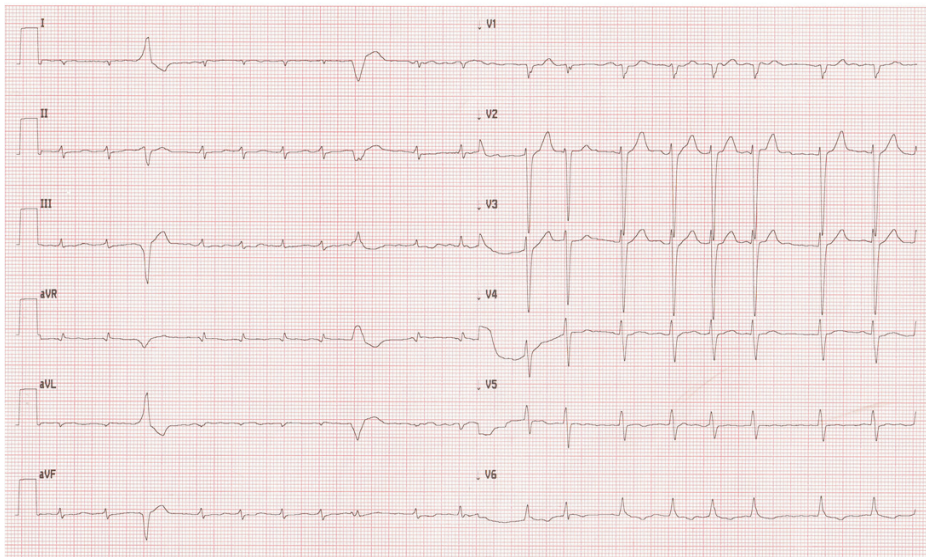


Fig. 3. Electrocardiogram of a patient with atrial fibrillation

fibrillation, supplementation with this cation is often used in the treatment and prevention of the recurrence of arrhythmia (DECARLI et al. 1985, REINHART et al. 1991). ONALAN et al. (2007) carried out a meta-analysis of 12 randomized controlled trials, comparing intravenous magnesium versus placebo or antiarrhythmic agents for the acute management of rapid atrial fibrillation. The analysis revealed that magnesium was effective in achieving the rate or rhythm control. Moreover, time to response was significantly shorter in the magnesium group while the risk of having a major adverse effect in the magnesium group was similar to that in the placebo group. Results of the meta-analysis data suggest that intravenous magnesium administration is an effective and safe strategy for the acute management of rapid atrial fibrillation (ONALAN et al. 2007). HO et al. (2007) carried out another meta-analysis of 10 randomized controlled trials, including a total of 515 patients with paroxysmal atrial fibrillation. The study revealed that intravenous magnesium was ineffective in converting atrial fibrillation to the sinus rhythm when compared to placebo or an alternative antiarrhythmic drug. However, compared to placebo, adding intravenous magnesium to digoxin increased the number of patients with a ventricular response <100 beats min^{-1} . Comparing to calcium antagonists or amiodarone, intravenous magnesium was less effective in reducing the ventricular response but also less likely to induce significant bradycardia or atrioventricular block (HO et al. 2007).

According to Nair and Morillo, both meta-analyses show that magnesium does not have advantage over conventional atrioventricular node blockers (calcium antagonists, beta-blockers) and antiarrhythmic agents (amiodarone, class I drugs). However, magnesium is better than placebo, particularly in combination with digoxin, if the ventricular rate ≤ 100 min^{-1} is taken as a criterion of the effectiveness of atrial fibrillation acute treatment (NAIR, MORILLO 2007). It seems that the role of magnesium in atrial fibrillation is secondary and limited to cases in which antiarrhythmic drugs are contraindicated or ineffective.

Magnesium might also be useful in postoperative atrial fibrillation, the most common complication after coronary artery bypass grafting. The ESC guidelines for the management of atrial fibrillation emphasize hypomagnesaemia as an independent risk factor for postoperative atrial fibrillation (CAMM et al. 2010). Meta-analysis of seven double-blind, placebo-controlled, randomized clinical trials including 1,028 participants revealed that intravenous magnesium reduced the incidence of postoperative atrial fibrillation by 36%, encouraging the use of intravenous magnesium as an alternative to prevent postoperative atrial fibrillation after coronary artery bypass grafting (GU et al. 2012). Moreover, it was found that administration of potassium/magnesium solution had a beneficial effect on the success rate of external biphasic electrical cardioversion in patients with persistent atrial fibrillation (SULTAN et al. 2012). However, a study by FRICK et al., carried out on 170 patients with atrial fibrillation, revealed no influence of oral magnesium on

the recurrence rate of atrial fibrillation after elective cardioversion (FRICK et al. 2000, BRUGADA 2000).

The significance of magnesium deficiency in ventricular arrhythmias has not been as thoroughly investigated as in supraventricular arrhythmias, although it was shown that magnesium increases the threshold for both ventricular tachycardia (Figure 4) and ventricular fibrillation (GHANI, RABAH 1977). Based on few and haphazard clinical observations, it is difficult to draw firm conclusions and recommend magnesium therapy. The effects of magnesium and potassium supplementation in stable patients with big ($\geq 720/24$ h) ven-

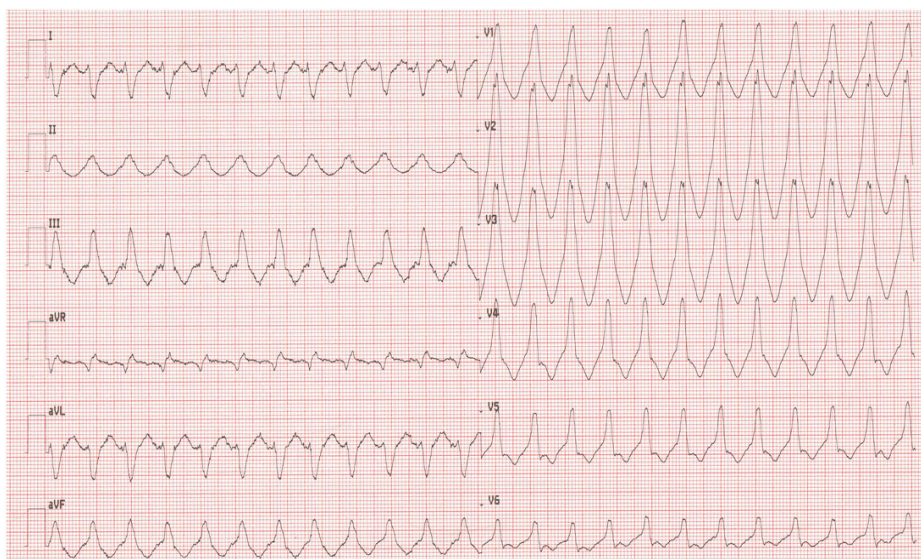


Fig. 4. Electrocardiogram of a patient with ventricular tachycardia

tricular arrhythmia were assessed in a randomized, double-blind controlled MAGICA trial. It was found that a 3-week oral treatment with 6 mmol of magnesium and 12 mmol of potassium significantly reduced the incidence of arrhythmia compared to placebo (ZEHENDER et. al. 1997). Despite such promising results, the authors limit the use of Mg/K as a therapeutic option only to non-life-threatening ventricular arrhythmias. The European and both American Cardiac Societies (ACC / AHA / ESC, 2006) recommend the use of Mg and K intravenously in severe cases or orally for chronic supplementation of patients with ventricular arrhythmias and to prevent sudden cardiac death, as such therapy has a beneficial effect on the electrophysiological substrate of ventricular arrhythmia (ZIPES et al. 2006). This treatment is especially suitable for counteracting magnesium and/or potassium deficiency and should be considered as a complementary therapy when normal concentrations of electrolytes are diagnosed.

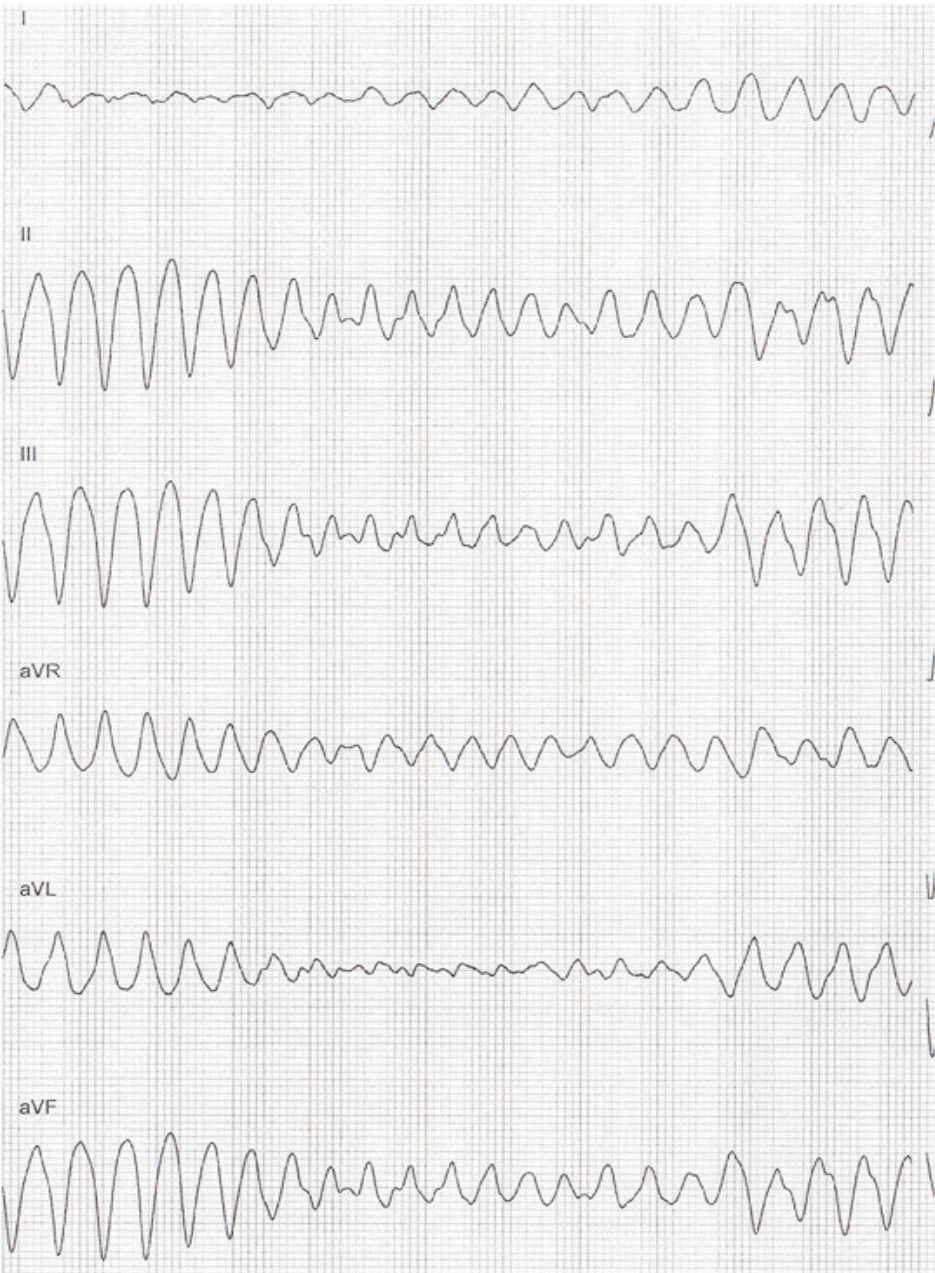


Fig. 5. Electrocardiogram of a patient with polymorphic ventricular tachycardia (torsade de pointes)

Polymorphic ventricular tachycardia (torsade de pointes; Figure 5) is an alternative form of ventricular tachycardia and can occur with or without QT prolongation. In cases with a normal QT interval, mostly induced by heart ischemia, antiarrhythmics (β -blockers, amiodarone) are recommended for therapy. In cases with a prolonged QT interval, the prolongation may be caused by antiarrhythmic drugs used in paroxysmal atrial fibrillation or by the deficiency of electrolytes. Then, administration of an intravenous bolus of magnesium effectively stops an attack of arrhythmia. Therefore, magnesium is recommended for the acute treatment of this form of arrhythmia (class IIa recommendation; ZIPES et al. 2006, HILTON et al. 1992).

CONCLUSIONS

Intravenous magnesium seems to be useful in prevention and treatment of various cardiac arrhythmias, being especially effective in cases of polymorphic ventricular tachycardia (torsade de pointes). Moreover, magnesium therapy is well-tolerated, with sporadic, mild and quickly subsiding adverse effects (heat, flushing, hypotension). Therefore, magnesium is a common component of a complex antiarrhythmic therapy. However, it should be noted that magnesium is not registered as an antiarrhythmic drug and should be treated rather as an adjuvant to antiarrhythmic therapy.

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