IS INTRAVENOUS MAGNESIUM EFFECTIVE IN CARDIAC ARRHYTHMIAS?

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ABSTRACT

Magnesium is the second most abundant intracellular cation with many control and regulatory functions. It regulates energy production and utilization and modulates activity of membrane ionic channels.
Magnesium has direct control effects on cardiac myocyte ion channels making it useful in certain arrhythmias. Calcium is responsible for pacemaker excitation and for excitation-contraction coupling in myocytes but increased intracellular calcium produces early and late afterdepolarisations initiating arrhythmias. Magnesium regulates calcium channel activity preventing raised intracellular levels. Potassium channel activity is enhanced by magnesium hyperpolarizing the cell reducing arrhythmia generation.
Magnesium is effective against long QT Torsade de Pointes. In rapid atrial fibrillation magnesium produces rate control slowing AV nodal conduction. Magnesium prevents digitalis toxicity due to associated hypomagnesemia.

Key words: Magnesium; Arrhythmias; Ion channels; Action potential; Ischemia

1. INTRODUCTION

Magnesium as in intracellular ion serves over 300 intracellular metabolic and regulatory functions. Within the cardiac system it is responsible for modulating mitochondrial metabolism, various membrane receptors and ion channels. It has both direct and indirect effects on the cardiac action potential which suggests its usefulness as an antiarrhythmic agent.

This article will explore the normal function of intracellular magnesium in cardiac cells in relation to electrophysiology. The role magnesium has on the various ion channels responsible for the myocyte action potential and in arrhythmogenesis will be reviewed. The use of intravenous magnesium in managing these arrhythmias especially Torsades de pointes, atrial fibrillation and digitalis toxicity will be discussed using latest evidence from literature.

2. METHOD

Although there are some small studies on magnesium's use in specific arrhythmia management none explore the broader use in cardiology. Therefore this literature review seeks to explore the current evidence for magnesium use in arrhythmia management and in its effects on cellular biochemistry which may highlight future possible research opportunities in clinical practice.
The following databases were searched for relevant texts: Science Direct, Ebsohost (Medline), Proquest, Oxford University Press and Pubmed. The key words used were: Magnesium, arrhythmias, antiarrhythmic, atrial fibrillation, Torsades de Pointes, digoxin and specific texts on magnesium in biochemistry for effects on each of the specific ion channels. All studies using both animals and humans were included. Review article reference lists were searched for further relevant texts.

3. MAGNESIUM IN CARDIAC CELLULAR PHYSIOLOGY

Magnesium is the second most abundant intracellular metal cation (positively charged ions) with concentrations between 0.4 – 1 mmol/L (Mubagwa *et al*, 2007). The concentration gradient of magnesium is about 10 mM intracellular to 1 mM extracellular (Wolf *et al*, 2003). It is associated with multiple intracellular functions: Transmembrane channel modulation, cellular energy production, synthesis of proteins and nucleic acids and enzyme activity (Saris *et al* 2000).

a. Magnesium as cofactor for many intracellular enzymes.

The most noted ionic function of magnesium is as cofactor on the enzyme Na^+-K^+ ATPase (Saris *et al*, 2000). This plays a role in activation and function of the Na^+-K^+ pump - an important part of repolarisation in phase 4 of the action potential. ATP binds to sites on the ion channels in the presence of Mg^{2+}. ATP is hydrolyzed to ADP with the release of P^+ providing energy to pump Na^+ against the concentration gradient (Lodish *et al*, 1995). Decreased intracellular sodium raises the concentration gradient across the cell membrane, providing the drive for the Na^+-Ca^{2+} exchanger. This reduces intracellular [Ca^{2+}] (Carmeliet, 1999).
Magnesium is also responsible for activating thiamine into thiamine pyrophosphate, modulating cellular metabolism of glucose in the production of intracellular energy substrate ATP (Johnson, 2001). Magnesium modulates the oxidant-antioxidant status, increasing antioxidant defense (Wolf *et al*, 2003).

b. Role of magnesium in effecting cardiac cellular ionic activity

Magnesium alters ions channels via four mechanisms: pore block, allosteric effects, modulation of enzymes or G-proteins and interacting with surface charges (Mubagwa et al, 2007). Pore block is voltage dependant and may produce altered direction of the current flow at positive voltages. Allosteric binding of Mg^{2+} takes place at alternative sites to the active sites and may

produce voltage independent modulation of currents. Mg^{2+} is needed to activate and terminate G-protein activity and thus regulates all ionic channels with such modulation. The cell membrane has fixed charges creating a surface potential. Magnesium can bind to these charges shifting voltage gating of the channel. Increased magnesium shifts the gating to more negative potentials and *vice versa (Mubagwa et al, 2007).*

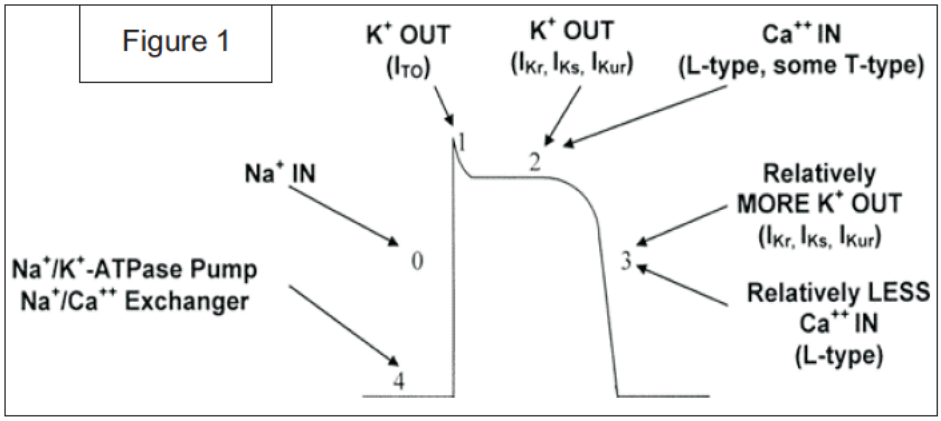
Mg^{2+} activates the Na^{+}-K^{+} ATPase thus regulating Na^{+} and K^{+} levels (Bers, Barry & Despa, 2002). Low Mg^{2+} and ATP both result in poor function of the pump thus decreasing intracellular Na^{+} and increasing K^{+} loss from the cell (via I_{k1}) (Bers, Barry & Despa, 2002; Ibarra, Morley & Delmar, 1991). Decreased intracellular Na^{+} may result in decreased $Na^{+}Ca^{2+}$ exchanger rate causing an increased intracellular Ca^{2+}.

Magnesium binds strongly to ATP and less strongly to ADP this being responsible for buffering Mg^{2+} therefore levels rise during low O_2 states (Saris *et al* 2000; Mubagwa *et al*, 2007; Delva, 2003) [see 2)c)v) below].

c. Magnesium effects on Cardiac cell electrolyte transportation

To understand magnesium's use in arrhythmia management its effect on the cardiac action potential needs to be explored. The cardiac action potential is comprised of four stages with each being regulated by various ion channel activity (See figure 1). The activity of each channel, magnesium's regulatory function and the stage in the action potential will be discussed later.

Figure 1



Adapted from Klabunde, R.E. Cardiovascular Pharmacology Concepts

i. Voltage de pendant Ca^{2+} channels

The L-type Ca channels are found in conductive tissue, atrial and ventricular myocytes (Brette *et al*, 2006). They are activated by the resting membrane potential becoming less negative and open on reaching threshold potential (Shorofsky & Balke, 2001). Calcium entry via the L-Type channels activates ryanodine receptors to release Ca^{2+} from the Sarcoplasmic Reticulum (SR)

(Meissner, 2004). Calmodulin is one of the regulators of Calcium induced Calcium release (CICR) from the SR via Ryanodine receptors (Meissner, 2004). After depolarization Ca^{2+} is either transported into the SR or out of the cell via the $Na^{+}Ca^{2+}$ exchanger (Klabunde, 2005). Decreasing the intracellular calcium influx has negative chronotropy (on pacemaker cells), ionotropy (on myocytes) and dromotropy (on the AV node) (Klabunde, 2005).

Increased intracellular Ca^{2+} is linked to early (EAD) and delayed afterdepolarisations (DAD) thus increasing the risk of arrhythmogenesis (Aomine *et al*, 1999). EAD are thought to arise from spontaneous release of Ca^{2+} from the SR and inward flow of Na^{+} Ca^{2+} channels. The current is uniform across the cell membrane (Boyden & ter Keurs, 2005). These abnormal currents are seen more when the Action Potential is prolonged. This can result from hypokalemia, hypomagnesemia and bradycardia (Akar & Tomaselli, 2004). DADs are propagated by transient spontaneous Ca^{2+} inflow in a focus within the cell – the so called Ca^{2+} spike. This focus activates local ryanodine receptors and sets up a Ca^{2+} wave across the cell. If the cell Ca^{2+} concentration is high this may cause threshold to be reached with subsequent depolarization (Boyden & ter Keurs, 2005)

L-type Ca^{2+} channels studied in rats showed suppression by magnesium at physiological levels increasing especially in the upper range (Wang, Tashiro & Berlin, 2003; Shorofsky & Balke, 2001). This suppression can be in two forms: physiological with magnesium entering and slowing conduction through the channel; or by increased extracellular concentration thus altering membrane polarization (Delva, 2003). Increased MgATP on the other hand has been linked to greater Ca^{2+} channel opening and longer action potential duration (Shorofsky & Balke, 2001)

Both Magnesium and calmodulin block the CICR at higher intracellular Ca^{2+} levels. Mg^{2+} competes for the Ca^{2+} binding site thus relying on high intracellular levels to achieve the block (Meissner, 2004). L-type Ca^{2+} currents conducted through the AV node can be slowed using magnesium or Calcium channel blockers (Shorofsky & Balke, 2001; Brette *et al*, 2006). Thus potentially in hypomagnesaemia the negative chronotropic effect of magnesium is decreased predisposing to conduction of tachyarrhythmias. This mechanism may be important in rapid Atrial Fibrillation (Shorofsky & Balke, 2001; Davey & Teubner, 2005). Magnesium is therefore useful to slow AV conduction in all supraventricular tachyarrhythmias. [See 4) below].

ii. T type Calcium channels

These are found primarily in nodal tissues (Mubagwa *et al*, 2007). They are thought to play a role in spontaneous depolarization and thus pacemaker function within the SA and AV nodal tissues (Klabunde, 2005). These channels are not found in human atrial or ventricular tissues (Perez-Reyes, 2003). The expression of T type channels is highest in neonatal hearts of all species declining into adulthood (Vassort, Talavera & Alvarez, 2006).

Smaller animal species also have greater expression of these channels (Vassort, Talavera & Alvarez, 2006) possibly due to the faster heart rates required. The activity of these channels is most pronounced at low voltage levels (activation around -50mV with peak around -30 to -20mV) (Vassort, Talavera & Alvarez, 2006). The T type current is a small burst Ca^{2+} spike theorized to activate Na^{+}-Ca^{2+} exchanger currents to bring the cell to threshold (Vassort, Talavera & Alvarez, 2006).

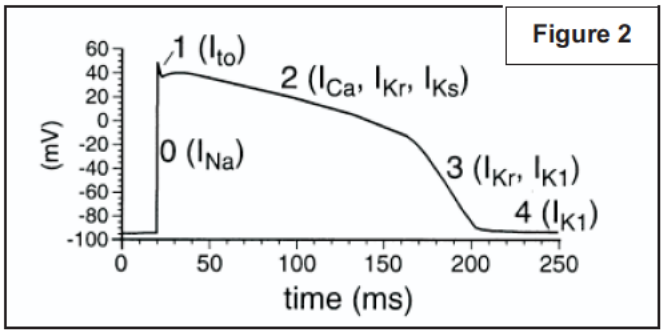
Their expression increases early in certain cardiac conditions like heart failure (Perez-Reyes, 2003; Vassort, Talavera & Alvarez, 2006). Their numbers increase with exposure to increased aldosterone resulting in increased heart rate and arrhythmias. This may result in EAD and DADs propagation (Vassort, Talavera & Alvarez, 2006)

Spironolactone is an aldosterone antagonist and is shown to prevent magnesium loss in heart failure. This was associated with fewer arrhythmias and slower resting heart rates (Gao *et al*, 2007). Physiological levels of Mg^{2+} were found to produce a moderate block of this current. This block had greater significance at more negative voltages (Serrano *et al*, 2000). Blocking the T Type channel current may reduce rate by slowing spontaneous depolarization.

iii. Inward rectifier K^{+} channels

I_{K1} channels are found in greater numbers in atrial and ventricular contractile cells and ventricular conducting tissue than in the nodal cells (Mubagwa *et al*, 2007). During phase 3 of the action potential I_{K1} outward K^{+} currents are responsible for late repolarisation and maintain the resting membrane potential in phase 4 [see Figure 2] (Mubagwa *et al*, 2007). During phase 2 of the action potential there is a cross- over period of inward current caused by Mg^{2+} (Rees, 1996) or intracellular amines spermine and spermadine (Lopatin & Nichols, 2001). This inward current maintains the plateau and with Ca^{2+} lengthens the action potential (Lopatin & Nichols, 2001). This is more pronounced in ventricular than atrial tissue (Lopatin & Nichols, 2001).

The outward current is decreased by magnesium deficiency thus precipitating a less negative resting membrane potential (Delva, 2003). This may be due to upregulation by PKA (cAMP regulated Protein Kinase) which needs MgATP or free Mg^{2+} (Lopatin & Nichols, 2001). This may predispose to automaticity with subsequent arrhythmias [see 4 below].

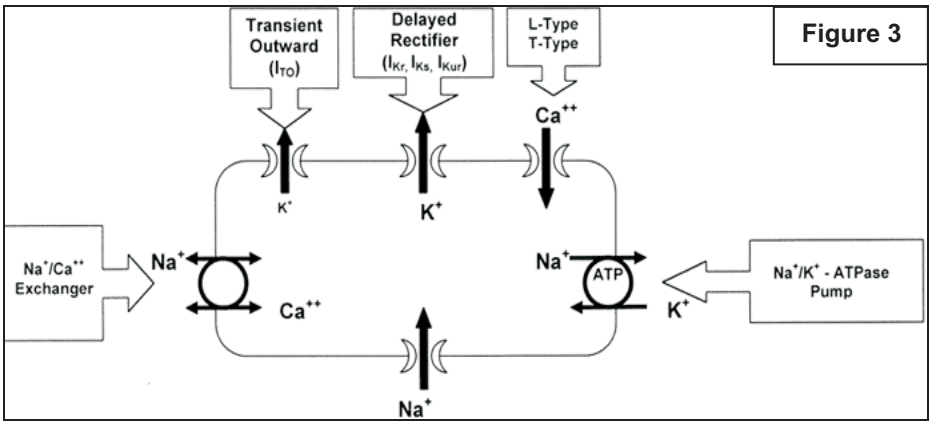


iv. Delayed rectifier I_K channels

I_K channels are responsible for the phase 3 repolarisation of the cardiac cell (Klabunde, 2005). These channels are found in both cardiac and vascular smooth muscle cells. There are three distinct currents I_{Kr} (for rapid), I_{Ks} (for slow) and I_{Kur} (for ultrarapid) (Tamargo *et al*, 2004) [see figure 3]. I_{Kur} is responsible for atrial repolarisation therefore shortening atrial action potential (Tamargo *et al*, 2004). I_{Kr} is found in greater numbers in human ventricular tissue and is responsible for phase 3 repolarisation current (Tamargo *et al*, 2004). I_{Ks} are slow to open at higher voltages and slow to deactivate thus playing an important role in action potential duration shortening during faster heart rates (Tamargo *et al*, 2004).

Homogeneous K_v channels in rat aortic smooth muscle cells with were studied at varying Mg^{2+} concentrations (Tammaro *et al*, 2005). Magnesium had the effect of 'voltage dependant inactivation to more negative voltages' and increased inward rectification at higher voltages lengthening the action potential and hyperpolarizing the cell (Tammaro *et al*, 2005).

A similar effect was noted on the I_K channels affecting all three types (Tamargo *et al*, 2004). The effect of this is to lengthen action potential duration but may precipitate long QT. In a study using Mg^{2+} free solution the I_K current initially increased then tapered to no flow suggesting Mg^{2+} is required to maintain the working of the channels (Tamargo *et al*, 2004). From this can be deduced that magnesium exhibits a block at positive potentials and stimulates activity at more negative potential thus maintaining a stable resting membrane potential.



Adapted from Klabunde, R.E. Cardiovascular Pharmacology Concepts

v. Other K channels

K_{ATP} channels are sensitive to MgATP / MgADP ratios and open during times of hypoxia causing K^+ efflux and preventing Ca^{2+} accumulation in the cell (Alekseev *et al*, 2005). This serves a protective function as Ca^{2+} buildup can precipitate apoptosis (Wolf *et al*, 2003). Magnesium exhibits open channel block creating a weak inward rectification of the K_{ATP} channel (Tamargo *et al*, 2004; Mubagwa *et al*, 2007). Magnesium increases the inhibiting effect of ATP on the outward currents of K_{ATP}.

K_{Ach} channels are indirectly activated by magnesium through activation of the G-Protein on stimulation of Muscarinic or Adenosine receptors (Mubagwa *et al*, 2007). These channels are found mainly in SA and AV nodal tissue and purkinje cells in the ventricles (Mubagwa *et al*, 2007).

4. ISCHEAMIA AND ARRHYTHMIA GENERATION

Ischeamia triggers a chain reaction of intracellular metabolic changes affecting the structure of ion channels, reducing ATP production and activating increased formation of oxygen free radicals (Carmeliet, 1999). During hypoxia the cell begins conserving energy favouring production of lactate. Radicals inhibit Na^+ and K^+ currents, block the Na^+Ca^{2+} exchanger, Na^+K^+ ATPase pumps and cause Ca^{2+} leak currents making the cell sensitive to Ca^{2+} overload (Carmeliet, 1999). This Ca^{2+} sensitivity includes spontaneous release of Ca^{2+} from the SR producing DAD triggering arrhythmias (Shorofsky & Balke, 2001). Failure of the ATP Ca^{2+} pump to shift cytosolic Ca^{2+} into the SR may cause Ca^{2+} overload (Boyden & ter Keurs, 2005). This may be a primary mechanism in abnormal automaticity related arrhythmias (Boyden & ter Keurs, 2005). These currents may also initiate DAD and EAD triggered activity (Akar & Tomaselli, 2004).

K_{ATP} channels activated by either ATP depletion or free radicals cause K^+ outflow from the cell producing a cellular protective effect (Alekseev *et al*, 2005).

Repeated exposure to mild hypoxia produces ischaemic preconditioning. This response enables the cell to survive prolonged periods of ischeamia (Tamargo *et al*, 2004). Ischaemia produces two stages with distinct electropathological patterns (Carmeliet, 1999). In the first stage action potential velocity and amplitude are decreased with a prolonged plateau. EAD and DAD are noted with prolonged phase 3 repolarisation, shortened absolute and lengthened relative refractory periods (Carmeliet, 1999; Shorofsky & Balke, 2001). In stage two the cell depolarizes and exhibits short action potentials, finally hyperpolarizing and developing irreversible contracture (Carmeliet, 1999).

5. MAGNESIUM AND ARRHYTHMIAS

Hypomagnesaemia has been linked to enhanced 'automaticity and triggered mechanism' (Gao *et al*, 2007) Automaticity is the ability of cells to spontaneously depolarize to threshold level producing action potential (Akar & Tomaselli, 2004). Triggered mechanism (DAD or EAD) have previously been discussed (see 3) above). The third and most common mechanism of arrhythmia is reentry where propagation occurs around an inexcitable obstacle. The circuit demonstrates a unidirectional block and slow conduction to allow recovery before the impulse conducts round again (Akar & Tomaselli, 2004).

Increased Intracellular Mg^{2+} (measured in erythrocytes) reduced the risk of premature ventricular ectopics, atrial fibrillation and tachycardia while slowing heart rates (Gao *et al*, 2007). There was no correlation with plasma magnesium levels to reduced arrhythmia risk (Gao *et al*, 2007). Aomine *et al* (1999) found that increasing extracellular magnesium to 10 mM (normal about 1mM) in rat papillary muscles and guinea pig ventricular cells demonstrated a complete block of DAD, EAD and triggered activity. Magnesium has been trialed in reentrant Supraventricular Tachycardias with mixed success (Delva, 2003). The mechanism being linked to its ability to slow AV conduction (see 3)c)i) above).

a. Torsades de pointes (TdP)

TdP can be as a result of drug effects, electrolyte deficiencies or congenital long QT syndrome (Gowda *et al*, 2004; Gupta *et al*, 2007). Long QT syndrome is a primary cause of TdP (Gupta *et al*, 2007). Blocking the I_{Kr} current leads to delayed repolarisation and lengthened QT interval (Gowda *et al*, 2004). EAD and heterogeneous refractoriness may lead to unidirectional block, re-entry circuit and onset TdP (Gupta *et al*, 2007; Akar & Tomaselli, 2004). TdP may be self-limiting or may degenerate into VF, which is a major safety concern of any drug which prolongs QT interval (certain antibiotics, second generation antihistamines, antiarrhythmics and antipyschotics) (Gowda *et al*, 2004).

Verduyn *et al* (1997) demonstrated significant shortening of the QT, reduced or suppressed EAD and suppressed ectopic beats in dogs using magnesium IV infusion. 10 mM Magnesium added to the solution completely abolished EAD and DAD in Guinea Pig ventricular cells (Aomine *et al*, 1999). Magnesium is only effective against long QT TdP (ILCOR, 2005). There are only small observational

studies looking at the efficacy of magnesium in TdP management but it appears safe to use in conjunction with other therapies (ILCOR, 2005).

b. Atrial Fibrillation (AF)

Atrial fibrillation is a common arrhythmia with clinically significance. In 60 – 70% of patients it may be associated with rapid ventricular response which requires rate control (Khan *et al*, 2004). Fast ventricular rates limit diastolic filling time thus decreasing stroke volume and so reducing cardiac output (Khan *et al*, 2004). This rapid ventricular rate may lead to left ventricular failure if not managed (Davey & Teubner, 2005). The primary goal of rapid AF management is rate control as cardioversion to normal sinus rhythm without anticoagulation is associated with thromboembolic risk (ILCOR, 2005).

Magnesium is one of the drugs noted for rate control of rapid atrial fibrillation (ILCOR, 2005). Mg^{2+} decreases AV nodal transmission thus helping to slow the rapid AF (Davey & Teubner, 2005).
Onalan et al (2007) conducted a meta-analysis of 8 low powered randomised control trials of magnesium used in atrial fibrillation (double blind and non blinded studies). In a total patient number of 303 (154 Mg^{2+} and 149 control) the effectiveness was statistically significant for rate control (OR 1.96, 95% CI 1.24 to 3.08) (Onalan *et al*, 2007). Magnesium also demonstrated rhythm control (OR, 1.60, 95% CI 1.07 to 2.39) (Onalan *et al*, 2007) which would not be the initial result desired in prolonged AF (greater than 48 hours). The study by Davey & Teubner (2005) contributed the largest patient cohort to the meta-analysis (46.59%) (Onalan *et al*, 2007).

Although Davey and Teubner (2005) found a 31% increase in rate control (pulse below 100 bpm) in the study group compared to placebo (RR 1.89; 95% CI 1.38 to 2.59; P<.0001) magnesium was used in conjunction with other antiarrhythmics so the effect cannot be directly attributed to magnesium. A comparison of magnesium to diltiazem in paroxysmal AF showed similar efficacy with a tendency for magnesium to more consistently restore sinus rhythm by 6 hours (P<0.001) (Chiladakis *et al*, 2001).

c. Digitalis toxicity induced arrhythmias

Digitalis works by blocking Na^+K^+ ATPase channels thus increasing the inward Na^+ current. This increases the Na^+Ca^{2+} exchanger current increasing intracellular Ca^{2+} and improving excitation-contraction coupling and cardia output (Lodish *et al*, 1995).

Increased intracellular Na^+ and Ca^{2+} and decreased K^+ creates resting membrane instability. This leads to automaticity and the lengthening of the action potential duration with DAD and EAD formation (Dawson & Buckley, 2007)

Hypomagnesaemia has been recognized as a precipitating factor for digoxin toxicity even in normal therapeutic ranges (Cohen & Kitzes, 1983). As noted previously magnesium suppressed EAD and DAD at higher levels (See 4 above). Magnesium enhances I_K currents at negative voltages thus suppressing automaticity in ventricular tissue (see 2)c)iv) above)

6. CONCLUSION

Magnesium plays a vital role in many intracellular functions. It modulates cardiac ion channels via direct or indirect mechanisms. Mg^{2+} regulates ATPase activating membrane electrogenic pumps. It inhibits L-Type Ca^{2+} channels and Ca^{2+} release from the SR. There is only a weak inhibition of T-Type Ca^{2+} channels. Magnesium causes inward rectification in I_{K1} channels by pore block. The delayed I_K channels are blocked at positive voltages but enhanced at negative voltages.
Ischeamia sets up a chain reaction altering ionic currents and producing the substrate for arrhythmias. Automaticity, triggered activity and reenty mechanisms occur due to ion current shifts. Magnesium has been shown to block triggered activity – the primary cause of TdP and AF. It provides rate control in AF and stops certain SVTs. In a meta-analysis of Mg^{2+} use in AF it provided rate control and rhythm control but both with wide confidence intervals. It suppressed arrhythmias from digitalis toxicity through the Na^+K^+ ATPase pump enhancement. Magnesium's role in intracellular management is well established in animal and human tissue laboratory studies. There is sparse clinical trial evidence to support its routine primary use except in TdP. As more evidence of magnesium's role in intracellular control is discovered we may see an increased use either alone or in conjunction with other antiarrhythmics.

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