Intravenous MgSO₄ alone and in combination with glucose, insulin and potassium (GIK) prolong the atrial cycle length in chronic atrial fibrillation

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Department of Cardiology, Lund University, Lund, Sweden

**Aims** To investigate the effects of parenteral administration of MgSO₄, and glucose, insulin, and potassium (GIK), on the dominant atrial cycle length during chronic atrial fibrillation (CAF).

**Methods and Results** The length of the dominant atrial cycle (DACL) in the power–frequency spectrum of the QRST-suppressed lead V₁ ECG was identified before and after intravenous administration of MgSO₄ alone and after 5 and 10 h of MgSO₄ and GIK infusion, in 13 patients with CAF. The changes in DACL were compared with changes in heart rate (HR), blood pressure and blood parameters. MgSO₄ alone increased the DACL from 146(13) (mean(SD)) (control) to 153(14) ms (P<0·01) and decreased the HR from 102(22) to 95(18) beats.min⁻¹ (P<0·05). After 5 h of MgSO₄ and GIK infusion the DACL was increased compared with control, from 146(13) to 152(11) ms (P<0·01), but unchanged compared with that after the bolus infusion of MgSO₄. HR was decreased compared with control (102(22)) and the bolus infusion of MgSO₄ (95(18)) to 87(15) beats.min⁻¹ after 5 h of intervention. The DACL was further increased after 10 h of MgSO₄ and GIK infusion compared with both control (from 146(13) to 157(11) ms), (P<0·01) and the 5 h infusion (152(11) to 157(11) ms), (P<0·05). No further changes were seen in HR after 10 h (87(17)) of intervention. There were indications of an inverse relationship between total changes in HR (ΔHR) and DACL (ΔDACL) during the interventions (P<0·05).

**Conclusion** Bolus infusion of MgSO₄ prolongs the DACL and decreases HR in CAF. A further prolongation of DACL was seen after 10 h of MgSO₄ and GIK infusion compared with control and with 5 h of intervention. Changes in DACL and HR during the entire intervention period showed an inverse relationship. The antiarrhythmic properties of MgSO₄ and the GIK solution in CAF clearly require further attention.

**Key Words:** Atrial fibrillation, magnesium, glucose, potassium, insulin, calcium channel, membrane potential, atrial remodelling.

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**Introduction**

Although chronic atrial fibrillation (CAF) is one of the most common sustained cardiac arrhythmias known in man, the atrial myocardial cellular patho-electrophysiological mechanisms involved in its initiation and propagation have not yet been satisfactorily clarified[1]. According to the multiple wavelet hypothesis, it is defined as a re-entrant arrhythmia, with continuous propagation of multiple, individual, re-entrant circuits or wavelets that simultaneously activate various parts of the atrial muscle. This theory was proposed as early as the 1950s[2] and verified in both animal experiments[3] and in-vivo studies, on induced[4] as well as spontaneously occurring AF during open heart surgery[5,6]. The theoretical wavelength of an individual wavelet is defined as the distance travelled by the depolarization wave during its refractory period and is calculated from the product of conduction velocity and the refractory period[7,8].

Our understanding of the atrial myocardial cellular patho-electrophysiology associated with CAF has grown considerably in recent years. Thus, in addition to the partially depolarized resting membrane potential in the fibrillating atrial myocardium, documented by several authors[9–15], recent studies have verified a rate-induced cytosolic calcium overload[16–19]. Both these mechanisms result in a decrease in atrial refractoriness, thereby enhancing its propensity for fibrillation[20].
These basic pathoelectrophysiological atrial defects may, to a certain extent, be counteracted by Mg\(^{2+}\) and glucose-insulin-potassium (GIK), acting via interference with the intracellular Ca\(^{2+}\) release mechanism\(^{[21,22]}\) and transmembrane transfer of potassium, respectively\(^{[23–25]}\).

Based upon these assumptions, the aim of the present study was to investigate whether MgSO\(_4\) alone and in combination with the GIK solution could affect the atrial cycle length during CAF in the intact human heart.

We have recently shown that the atrial component in the surface ECG of patients with CAF contains information that can be extracted to assess the dominant atrial cycle length (DACL)\(^{[26]}\). By use of this new, non-invasive method, we investigated changes in the DACL after bolus infusion of MgSO\(_4\) and during a 10 h maintenance infusion of MgSO\(_4\) and GIK solution in patients with CAF.

The investigation conforms with the principles outlined in the Declaration of Helsinki, and the study was approved by the Ethical Committee of the Medical Faculty, Lund University, Sweden, approval number LU 15–96.

**Methods**

**Patient selection**

Fourteen patients with CAF were recruited to the study. One was later excluded with alternation between AF and atrial flutter. The study group was composed of ten men and three women, with an age range 55–78 (mean 70) years (Table 1). Both pharmacological and electrical treatment had been unsuccessful. All patients included had an AF duration that exceeded 2 months. All anti-arrhythmic treatment, including digoxin, was withdrawn at least 5 T\(_{1/2}\) before participation in the study. Patients with diabetes mellitus, hyperthyroidism, hepatic diseases, renal failure, infections or electrolyte disturbances were excluded.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age [years]</th>
<th>Sex</th>
<th>AF associated disease</th>
<th>AF duration [month]</th>
<th>Mg given [mmol.l(^{-1})]</th>
<th>Mg excreted [mmol.l(^{-1})]</th>
<th>Mg retained [mmol.l(^{-1})]</th>
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<tr>
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HT=hypertension, IHD=ischaemic heart disease, MVD=mitral valve disease, AF=atrial fibrillation, M=male, F=female. Retained magnesium was calculated as the difference between total given dose of MgSO\(_4\) during the interventions and excreted dose, measured in urine collected during the entire intervention period. The mean amount of magnesium retained was 71%, i.e. 29% was excreted during the intervention period.

**Administration of MgSO\(_4\) and GIK solution**

The MgSO\(_4\) and GIK solutions were administered by infusion in a peripheral vein. The patients received MgSO\(_4\), 0·15 mmol.kg\(^{-1}\) as a bolus infusion in 250 ml glucose (50 mg.ml\(^{-1}\)) over a 10 min period, followed by MgSO\(_4\), 0·1 mmol.kg\(^{-1}\).h\(^{-1}\) in 1000 ml glucose (100 mg.ml\(^{-1}\)), 20 IU Actrapid (human insulin) and a KCl 40 mmol.l\(^{-1}\) (supplement) as a maintenance infusion over 10 h. The KCl supplement was excluded if the serum concentration of potassium (S-K) was equal to or greater than 4·0 mmol.l\(^{-1}\).

**Frequency analysis of the fibrillatory ECG (FAF-ECG)**

A new, non-invasive method based on frequency analysis of the f-waves in the surface ECG was used. The method is described in detail elsewhere \(^{[26]}\). In summary, the frequency distribution between 3 and 12 Hz in an ECG with a QRST-suppressed V\(_1\) lead, is estimated and the cycle length corresponding to the dominant frequency peak is named the dominant atrial cycle length (DACL) (Fig. 1). The changes in DACL induced by the interventions were noted and compared with changes in heart rate, blood pressure and blood parameters. The power–frequency spectrum was based on information from a 5 min ECG recording. Measurements were taken

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Table 1 Patient characteristics and magnesium turnover

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age [years]</th>
<th>Sex</th>
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HT=hypertension, IHD=ischaemic heart disease, MVD=mitral valve disease, AF=atrial fibrillation, M=male, F=female. Retained magnesium was calculated as the difference between total given dose of MgSO\(_4\) during the interventions and excreted dose, measured in urine collected during the entire intervention period. The mean amount of magnesium retained was 71%, i.e. 29% was excreted during the intervention period.
before the start, after the bolus infusion of MgSO₄ and after 5 and 10 h MgSO₄ and GIK infusions. Data acquisition was started after a 30-min resting period in all patients. Blood pressure was measured manually using a cuff sphygmomanometer at the time of ECG registration. Heart rate was calculated from the surface ECG recording.

**Laboratory analysis**

Serum concentrations of magnesium (S-Mg), potassium (S-K), sodium (S-Na), calcium (S-Ca, total) and free calcium ion (S-Ca²⁺ at pH=7.4), as well as S-pH and blood glucose (b-glucose), were measured. Measurements were performed before the start, 10 min after the bolus infusion of MgSO₄ and after 5 and 10 h of MgSO₄ and GIK infusion. Urine was collected throughout the 10 h intervention and U-Mg was calculated in the total amount of urine produced during this period.

**Statistical methods**

Data are expressed as means and standard deviations (SD) from the means in text and tables. Friedman’s test for repeated measurements was used for statistical evaluation of the whole group. Wilcoxon’s signed rank test was used as a post hoc test to evaluate the significance of changes within the groups. An analysis of covariance
Results

Control registration

Control values (mean(SD)) for DACL, heart rate, blood pressure and blood parameters are illustrated in Table 2. The control DACL had a mean of 146 ms and ranged between 119 and 165 ms. No correlation could be found between DACL and heart rate in the control situation.

Bolus infusion of MgSO4

None of the patients converted to sinus rhythm. All patients felt a transient sensation of warmth and flushing after the bolus infusion of MgSO4. One patient had additional symptoms attributable to hypotension and bradycardia. The DACL was increased in all cases after the bolus infusion of MgSO4, the mean value increasing from 146 ms to 153 ms (P<0.05) and from 152 to 157 ms (P<0.01), respectively. After the 10 h infusion the heart rate was unchanged compared with that after the bolus infusion of MgSO4 (Table 2). At 10 h the DACL was increased from 146 to 157 ms (P<0.01) and from 152 to 157 ms (P<0.05), compared with control and the 5 h infusion, respectively. The DACL after 10 h of infusion was unchanged compared with that after the bolus infusion of MgSO4 (Table 2) (Fig. 4).

Heart rate was significantly reduced after 5 h of MgSO4 and GIK infusion, compared with control and compared with after the bolus infusion of MgSO4, by 15 and 8 beats.min⁻¹ (P<0.01, P<0.05), respectively. After the 10 h infusion the heart rate was unchanged compared with after the 5 h infusion (Table 2). An inverse relationship was observed between total changes in heart rate (ΔHR) and DACL (ΔDACL) throughout the intervention (P<0.05 (Fig. 3). However, no statistically significant source of variation could be found for the relationship between ΔHR, ΔDACL, AS-Mg and AS-Ca²⁺, using all recordings, with ΔHR as dependent and ΔDACL, AS-Mg and AS-Ca²⁺ as covariates. Variation was allowed for patient and time point. There was no significant change in systolic or diastolic blood pressure, but the mean value for the former was reduced after the 5 and 10 h infusion, compared with control.

S-Mg increased further, from 1·62 to 2·12 mmol.l⁻¹ after the 5 h MgSO4 and GIK infusion (P<0.01), and to 2·32 mmol.l⁻¹ (P<0.05) after the 10 h infusion, rising continuously during the entire intervention period. Blood parameters are given in Table 2.

The total amount of magnesium retained after the entire intervention period, including the bolus infusion of MgSO4 and 10 h of MgSO4 and GIK infusion, was calculated from the difference between the magnesium given and excreted. A mean of 71% of given magnesium was retained. The amount of magnesium retained ranged between 95 and 48 mmol.l⁻¹ (Table 1).

Table 2 Effects of MgSO4 alone and MgSO4 and GIK solution in chronic atrial fibrillation

<table>
<thead>
<tr>
<th>Parameter measured</th>
<th>Control before infusion</th>
<th>Bolus infusion of MgSO4</th>
<th>5-h MgSO4 and GIK infusion</th>
<th>10-h MgSO4 and GIK infusion</th>
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</thead>
<tbody>
<tr>
<td>BP syst (mmHg)</td>
<td>148(15)</td>
<td>134(18)</td>
<td>137(24)</td>
<td>141(21)</td>
</tr>
<tr>
<td>BP diast (mmHg)</td>
<td>83(9-0)</td>
<td>82(9.3)</td>
<td>84(6-1)</td>
<td>82(8-3)</td>
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<tr>
<td>HR (beats min⁻¹)</td>
<td>102(22)</td>
<td>95(18)*</td>
<td>87(15)*</td>
<td>87(17)</td>
</tr>
<tr>
<td>DACL (ms)</td>
<td>146(13)</td>
<td>153(14)**</td>
<td>152(11)</td>
<td>157(11)*</td>
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<td>Magnesium (mmol.l⁻¹)</td>
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<td>1·62(0·29)**</td>
<td>2·12(0·21)**</td>
<td>2·32(0·40)**</td>
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<tr>
<td>Potassium (mmol.l⁻¹)</td>
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<td>Calcium (mmol.l⁻¹)</td>
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<td>2·23(0·08)**</td>
<td>2·16(0·11)**</td>
<td>2·04(0·14)**</td>
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<tr>
<td>Ca²⁺ (mmol.l⁻¹)</td>
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<td>1·15(0·04)**</td>
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<td>Sodium (mmol.l⁻¹)</td>
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<td>138(1·93)**</td>
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<td>Glucose (mmol.l⁻¹)</td>
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<td>5·38(1·30)**</td>
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<td>pH (Unit)</td>
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<td>7·41(0·03)</td>
<td>7·38(0·05)</td>
<td>7·41(0·04)</td>
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</table>

BP = blood pressure. HR = heart rate and DACL = dominant atrial cycle length. GIK = glucose, insulin and potassium. The Ca²⁺ values were standardized to pH=7·4. Values are presented as means (standard deviations from the means). *P<0.05, **P<0.01, all other changes were not statistically significant. Statistical evaluation was performed against the preceding value.

Bolus registration

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Figure 2  Changes in DACL in a single patient. The registrations were performed before intervention, after bolus infusion of MgSO₄ and after 10 h MgSO₄ and GIK infusion. The DACL prolongation, from 146 to 162 ms, corresponds to a change in frequency from 6.8 Hz to 6.2 Hz. Note the changes in amplitude and thickness of the frequency spectrum, which could represent a change from fine to coarse f-waves in the surface ECG, caused by the intervention.

Figure 3  There were indications of an inverse relationship between total changes in heart rate (ΔHR) and DACL (ΔACL) during the interventions (P<0.05). The plots represent the relationship of changes after the entire intervention period. In all patients except one there was a decreased heart rate and increased DACL, which suggests that the AV-nodal conduction time increases as the atrial cycle length increases. However, the patient with an increased heart rate had a decreased DACL.
The dominant atrial cycle length (DACL) in CAF

We have recently shown that the atrial component in the surface ECG of patients with CAF contains valuable information on the magnitude and dynamics of the atrial cycle length\[26\]. It was concluded that 5 min of ECG recording was sufficient for the DACL in lead V₁ to be reproducible, i.e. to capture the majority of the temporal dynamics of the DACL. It was verified that the right atrium is a major contributor to f-waves in lead V₁ and that the local cycle length, measured by right atrial intracardiac recordings, was in agreement with DACL measured at lead V₁. As several studies have verified that local fibrillation cycle lengths are related to the refractory period, the DACL of lead V₁ may be used as an index of right atrial refractoriness\[27–29\]. Further support for the use of DACL as an index of right atrial refractoriness has been obtained by studying the effects of dl-sotalol\[26\] as well as changes in the autonomic nervous discharge on DACL\[30\]. The resulting changes in DACL correspond to the anticipated changes, with these interventions, in the atrial refractory period during sinus rhythm. As the present study was not placebo-controlled, the influence of the autonomic nervous system (ANS) has to be considered. We have recently investigated the influence of the ANS on the DACL during CAF\[30\]. Increased sympathetic discharge provoked by tilt-testing thus shortened the average DACL by 10 ms, while the strong vagal discharge shortened the DACL by 15 ms. The tilt-provoked changes in the DACL were reversed after 5 min in the supine position. All recordings were performed after 30 min rest in the supine position\[30\].

Pharmacological effects of MgSO₄ infusion on the DACL in CAF

The intravenous infusion of MgSO₄ prolonged the DACL in all cases (Fig. 4), on average from 146 to 153 ms (P<0.01) and this was accompanied by an increase in the S-Mg level, from 0.9 to 1.62 mmol.l⁻¹ (P<0.01). The effects of Mg²⁺ are related to its ability to influence the movement of other ions across the sarcolemma of the atrial myocytes. The elevation in the S-Mg concentration could increase the atrial cycle length as a result of its ‘interference’ with the fine balance between inward Ca²⁺ and outward K⁺ currents during repolarization of the action potentials in the atrial muscle\[31–33\]. Whole-cell voltage–clamp recordings have shown that several K⁺ currents, especially the delayed rectifier (I_K) and the inward rectifier (I_{K1}) currents\[32,33\], are sensitive to increased extracellular concentrations of Mg²⁺, which will reduce the conductance of both channel currents. The I_K current is responsible for the resting membrane potential and the final repolarization in the atrial muscle\[30\]. Supernormal levels of Mg²⁺ act as an I_K1 channel blocking agent, to plug the open channel in a voltage dependent manner, and decrease the outward K⁺ current density. Translated into changes in action potential, a prolongation of the final repolarization will

Figure 4 Individual changes in the DACL during the interventions.
occur, accompanied by a slight depolarization of the atrial resting membrane potential. These changes will cause prolonged refractoriness and decreased conduction velocity in the atrial muscle, which in turn could increase the atrial cycle length.

Mg$^{2+}$ is a well-known calcium entry blocker of both L- and T-type calcium channels and reduces the Ca$^{2+}$ influx through these channels in atrial myocytes[21]. In contrast to the effects of Mg$^{2+}$ on outward K$^+$ currents, a reduced inward Ca$^{2+}$ current density will tend to shorten action potential duration[31]. Although the exact interplay between inward and outward currents during atrial repolarization in CAF is complicated, the total outcome of an elevation in S-Mg measured by FAF-ECG recording is a prolonged DACL.

Although other explanations cannot be excluded, the prolongation in DACL seen after the bolus infusion of MgSO$_4$ is probably caused by an increased refractoriness in the atrial myocytes. This interpretation is in agreement with some, but not all, studies on the effects of MgSO$_4$ on atrial myocardial refractoriness in patients with sinus rhythm[35-37].

The effects of MgSO$_4$ infusion on fibrillation-induced cellular calcium loading

The frequent and irregular depolarization of atrial myocytes during CAF may result in cytosolic calcium loading, which may in part be responsible for cellular patho-electrophysiological disturbances seen in atrial muscle[16-19]. Thus, it is possible that Mg$^{2+}$ may reverse cellular electrophysiological or ultrastructural changes in atrial myocytes induced by rate-related intracellular calcium overload. There are two major aspects to be considered concerning the potency of Mg$^{2+}$ in modulating intracellular calcium handling. Firstly, Mg$^{2+}$ reduces Ca$^{2+}$ influx in atrial myocytes via Ca$^{2+}$ entry blockades[22], which may reduce intracellular calcium overload. Secondly, although it is clear that cardiac cells are permeable to Mg$^{2+}$, the influx and efflux pathways and amounts of extracellular Mg$^{2+}$ needed for permeation to occur are still uncertain. However, an increased intracellular Mg$^{2+}$ concentration might have effects on cytoplasmic Ca$^{2+}$ handling, as several systems which buffer internal Ca$^{2+}$ levels may be Mg$^{2+}$-regulated[22]. The exact interplay between these effects requires further attention.

Atrial myocardial energy metabolism and the DACL

The rate of glucose transport over the cell membrane depends on the functional activity and the metabolic state of the atrial muscle[38]. It is known that glucose at supernormal levels, even without insulin, restores shortened atrial refractoriness in a metabolically depleted atrial muscle[39]. Interestingly, it seems that glucose does not affect single channel currents directly, but rather reinstates the metabolic deficit in the muscle by enhanced cellular glycolysis[39]. It is attractive to assume that the sustained rapid atrial rate during AF might reduce refractoriness through depletion of cytoplasmic adenosine triphosphate (ATP), with resulting activation of IKATP and perhaps other K$^+$ channels known to be activated during pathological conditions[34]. However, the contribution of the ATP-sensitive K$^+$ channel (IKATP) to cytoplasmic K$^+$ loss caused by metabolic rundown is still controversial, since it has not been proved that the cytoplasmic ATP level decreases to the level required for channel activation at the time when action potential shortening occurs. Furthermore, it may be that the ATP level needed for channel activation differs between intact atrial myocytes, myocytes in the fibrillating atrial myocardium and the myocytes in the patch configurations used in experimental studies. The selective IKATP blocker (glibenclamide) has been shown to have no effect on experimentally rate-induced shortening of atrial refractoriness, suggesting that activation of IKATP induced metabolic rundown does not contribute to electrical remodelling of the atrial muscle[47]. However, other studies have indicated that metabolic rundown could be involved in the basic patho-electrophysiological mechanisms associated with CAF in the intact human heart[39].

Although there are several possible explanations at the cellular level for the potential antiarrhythmic effect of maintenance MgSO$_4$ and a GIK solution during CAF, two aspects should be emphasized. Firstly, the increase in the atrial cycle length may be caused by the MgSO$_4$ infusion alone, as previously discussed. Secondly, the influence of the GIK solution on the atrial cycle length will depend on the metabolic state of the atrial myocytes in the fibrillating atrial myocardium, which requires further attention. However, the intervention seems to be favourable in view of the relationship between atrial size and the number of concomitant re-entrant wavelets possible, since the theoretical wavelength increases and a larger area of the atrium will be required to set up a re-entrant circuit[7,8,20].

Relationship between changes in heart rate and DACL during CAF

Both the bolus infusion of MgSO$_4$ and the maintenance infusion of MgSO$_4$ and the GIK solution resulted in a decreased heart rate, concomitant with a prolongation of the DACL, suggesting that the AV-nodal conduction time is increased as the atrial cycle length increases[40]. There were indications of an inverse relationship between the total changes in heart rate (ΔHR) and DACL (ΔDACL) throughout the intervention (P<0.05) (Fig. 3). Interestingly, there were indications of an opposite, inverse relationship between ΔHR and ΔDACL during increased sympathetic activity induced by head-up
MgSO₄ and GIK prolong the atrial cycle length in AF

The lack of a statistically significant contribution of change in ΔS-Mg and ΔS-Ca²⁺ may well be the small variation in the change between patients.

**Conclusion**

We conclude that a bolus infusion of MgSO₄ prolongs the DACL and decreases heart rate in CAF. A further prolongation of DACL was seen after 10 h of MgSO₄ and GIK infusion compared with control and prolongation of DACL was seen after 10 h of the intervention. The anti-arrhythmic potential of the MgSO₄ and GIK solution in CAF clearly motivates further attention.

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**References**


