Electrocardiographic Abnormalities and Serum Magnesium in Patients With Subarachnoid Hemorrhage

Walter M. van den Bergh, MD; Ale Algra, MD, FAHA; Gabriël J.E. Rinkel, MD, FAHA

Background and Purpose—ECG abnormalities and hypomagnesemia frequently occur after aneurysmal subarachnoid hemorrhage (SAH). Because hypomagnesemia is associated with several ECG abnormalities, we studied whether hypomagnesemia mediates ECG abnormalities after SAH.

Methods—We prospectively studied a consecutive series of 62 patients admitted within 72 hours after aneurysmal SAH. A standard 12-lead ECG and serum magnesium measurement were routinely performed at admission. The relationship between serum magnesium and ECG abnormalities was assessed with linear regression analysis and the Mann-Whitney test in case of dichotomized ECG abnormalities.

Results—Hypomagnesemia was present in 23 patients (37%), and 38 patients (61%) had a long QTc duration. Low serum magnesium was related to a long PR interval (P=0.001) and a shorter QTc interval (P=0.004). Adjustment for World Federation of Neurological Surgeons score, hydrocephalus, and the amount of cisternal and ventricular blood did not influence these relations.

Conclusions—In patients with SAH, lower serum magnesium levels are related to less pronounced increase in the QTc interval. Although the direction of the relation was unexpected, decreased serum magnesium might be the missing link between SAH and ECG abnormalities. (Stroke. 2004;35:644-648.)

Key Words: electrocardiography • long QT syndrome • magnesium • subarachnoid hemorrhage

Electrocardiographic abnormalities frequently occur after aneurysmal subarachnoid hemorrhage (SAH). Changes in ST segment (15% to 51% of patients), T waves (12% to 92%), prominent U waves (4% to 47%), QT prolongation (11% to 66%), and sinus dysrhythmias are the most common.1–3 ECG abnormalities usually disappear within a day with no any change in the neurological or cardiac condition.4–7 They are considered markers of the severity of the SAH but not predictors for potentially serious cardiac complications or clinical outcome.1,8,9

The pathophysiology of these ECG abnormalities is unsettled; one explanation is sustained sympathetic stimulation that results in structural damage to the myocardium.10–12 This sympathetic stimulation may in turn be mediated through an arrhythmogenic center in the insular cortex.3,11

We recently found that more than one third of patients with SAH have hypomagnesemia at admission and that hypomagnesemia is related to the extent of the hemorrhage.14 Magnesium depletion in general is associated with changes in the ECG. Widening of the QRS complex and peaking of T waves have been described with modest magnesium loss, whereas more severe magnesium depletion can lead to prolongation of the PR and QT intervals, progressive widening of the QRS complex, and diminution of the T wave.15

The aim of this study is to investigate the relation between serum magnesium depletion after SAH and the occurrence of ECG abnormalities and dysrhythmias after SAH.

Patients and Methods

We prospectively studied a consecutive series of 62 patients with aneurysmal SAH admitted within 72 hours to the University Medical Center Utrecht. This time frame was chosen because the most pronounced ECG changes occur during the first 72 hours.1 An ECG was routinely done at admission, as was blood sampling, which included measurement of magnesium and potassium. We used only the first ECG recording data from the initial blood sampling in our analyses. Hypomagnesemia was defined as serum magnesium <0.70 mmol/L.

The diagnosis of SAH was based on the presence of extravasated blood in the basal cisterns. Conventional or CT angiography was performed to detect an aneurysm. We included patients who had died before (CT) angiography could be performed only when the pattern of hemorrhage on the CT scan suggested an aneurysmal origin.

Clinical condition on admission was assessed by means of the World Federation of Neurological Surgeons (WFNS) scale, a 5-point scale based on the Glasgow Coma Scale, and the presence or absence of focal deficits.16

We assessed the amount of cisternal (range, 0 to 30) and ventricular (range, 0 to 12) blood on the initial CT scan according to the method described by Hijdra et al.17 For assessment of hydrocephalus, we quantified the size of the frontal horns by means of the bicaudate index. To calculate age-adjusted relative sizes, the bicau-
date indexes were divided by the corresponding upper limit per age group.18

ECG Analysis
ECGs were analyzed for heart rate, PR- and QTc- (heart rate–corrected QT)19 interval duration, width of the QRS complex, ST-segment depression or elevation, T-wave abnormalities, U-wave presence, and left ventricular hypertrophy. ECG abnormalities were defined according to the following established criteria: sinus bradycardia, sinus rhythm <60 bpm; PR-interval prolongation, duration >200 ms; QRS widening, QRS duration >100 ms; QTc prolongation, duration >440 ms; ST-segment depression, horizontal or downsloping ST segment with (≥0.05 mV) or without ST-J depression; ST-segment elevation, upward convexity of the ST segment (≥0.1 mV) with or without ST-J elevation; T-wave abnormalities, T waves that are of low voltage or are flat or inverted in leads in which they are normally upright or that are abnormally tall and peaked; prominent U wave, top >25% of the highest T wave in precordial leads; and left ventricular hypertrophy, S v1/v2 ≥3.5 mV (voltage criteria only)20; in men, R v5/v6 ≥3.5 mV; in women <40 years of age, T v1 ≥0.2 mV; in men >40 years of age, T v1 ≥0.2 mV; in women, T v1+T v5 ≥2.5 mV (or >1.2 or T v1 >0 mV in women <40 years of age); and in women >40 years of age, T v1 ≥0.2 mV.21,22

Data Analysis
The relation between serum magnesium and ECG abnormalities was assessed with linear regression in which ECG abnormalities were taken as the dependent variable. Regression coefficients (B) have to be interpreted as the amount of change in the dependent variable for a 1-unit increase in serum magnesium; corresponding 95% confidence intervals (CIs) were calculated. The QTc interval normally lengthens with age. Because of a relative shortening of the QTc interval in men during adolescence, it is longer in adult women than in men.23 For that reason, analyses for the QTc interval were adjusted for age and sex. The nonparametric Mann-Whitney test was used in case of dichotomized dependent variables (U wave, ST segment, T wave, left ventricular hypertrophy, and ischemia). All analyses were also performed for serum potassium.

Results
Patient characteristics and the occurrence of ECG abnormalities and hypomagnesemia are shown in Table 1. Hypomagnesemia was present in 23 patients (37%), and 38 patients (61%) had a long QTc duration. Malignant ventricular arrhythmias like torsade de pointes and ventricular fibrillation were not documented in our study population.

The relations between serum magnesium and ECG abnormalities are shown in Table 2. Low serum magnesium was related to a prolongation of the PR interval (B = −79; 95% CI, −126 to −31) (Figure 1) and a shorter QTc interval (B = 150; 95% CI, 50 to 249) (Figure 2). Adjustment for age and sex did not essentially influence these relations. There was a marginally significant relation with low serum magnesium and the presence of U waves (P = 0.048), but U waves occurred in only 2 patients.

Although hypokalemia at admission occurred in 17 patients (27%), serum potassium was not associated with hypomagnesemia or ECG abnormalities. Adjustment for potassium did not influence the relation between serum magnesium and ECG abnormalities.

Adjustment for clinical condition at admission, hydrocephalus, or the amount of cisternal and ventricular blood did not influence the relation between serum magnesium and ECG abnormalities (Table 3).

Discussion
The high frequency of ECG abnormalities in our study population is in line with the frequency reported in the literature.24 Prolongation of the QTc interval was the most common abnormality (61%); the mean QTc (460 ms) in our series of patients was even above the cutoff point at which

| TABLE 1. Patient Characteristics and ECG Abnormalities in 62 SAH Patients |
|------------------|-----|-----|
| Characteristics | n (%) |
|------------------|-----|-----|
| Female sex | 43 (70) |
| Poor WFNS | 25 (40) |
| Hydrocephalus | 22 (36) |
| Hypomagnesemia | 23 (37) |
| Bradycardia | 15 (24) |
| Long QTc | 38 (61) |
| Long PR | 4 (7) |
| Short PR | 8 (13) |
| Long QRS | 10 (16) |
| T-wave abnormality | 15 (24) |
| ST-segment abnormality | 18 (29) |
| Prominent U wave | 2 (3) |
| LVH | 9 (15) |

LVH indicates left ventricular hypertrophy.

<p>| TABLE 2. Relationship Between Serum Magnesium and ECG Characteristics |
|------------------|-----|-----|</p>
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>B*</th>
<th>95% CI</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>5</td>
<td>−50 to 59</td>
<td></td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>−79</td>
<td>−126 to −31</td>
<td></td>
</tr>
<tr>
<td>QTc interval, ms</td>
<td>150</td>
<td>50 to 249</td>
<td></td>
</tr>
<tr>
<td>QRS interval, ms</td>
<td>6</td>
<td>−15 to 27</td>
<td></td>
</tr>
<tr>
<td>T-wave abnormality (y/n)</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-segment abnormality (y/n)</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prominent U wave (y/n)</td>
<td>0.048</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy (y/n)</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Linear regression coefficient: change in ECG characteristic per 1-mmol increase in magnesium.
†Based on the Mann-Whitney test.
decrease in serum magnesium after SAH is cellular influx, the hypomagnesemia. The most plausible explanation for the finding that low serum magnesium was frequent and similar to the results of our previous study. The presence of hypomagnesemia after SAH was frequent and similar to the results of our previous study.14

**QTc Interval**

Both hypomagnesemia and a long QTc interval were very frequent after SAH, but in contrast to our hypothesis, low serum magnesium was related to a less prolonged QTc interval despite the fact that hypomagnesemia is a well-known cause for an acquired prolonged QTc interval.26 The explanation for the finding that low serum magnesium was not related to QTc prolongation perhaps lies in the cause of the hypomagnesemia. The most plausible explanation for the decrease in serum magnesium after SAH is cellular influx, which may increase not only cerebral27 but also cardiac intracellular magnesium.28,29 This might be an essential difference with the long QT syndrome caused by chronic magnesium depletion in which the total magnesium storage is depleted.

The cause of the initial prolongation of the QTc interval after SAH remains unclear. We will discuss 3 possible mechanisms. First, there is no causal relation between hypomagnesemia and ECG abnormalities after SAH. SAH causes a decrease in serum magnesium and ECG abnormalities simultaneously. However, adjustment for baseline characteristics (ie, WFNS score, amount of blood) for the relation between serum magnesium and QTc would then have a marked influence on this relation. Because this is not the case, a causal relation between serum magnesium and QTc interval is more probable.

**TABLE 3. Relationship Between Serum Magnesium and PR and QTc Intervals After Multivariate Adjustment for Sex, Age, WFNS Score, and Amount of Cisternal and Ventricular Blood and Serum Potassium**

<table>
<thead>
<tr>
<th>Characteristics B*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR interval</td>
<td>−74</td>
</tr>
<tr>
<td>QTc interval</td>
<td>156</td>
</tr>
</tbody>
</table>

*Linear regression coefficient: change in ECG characteristic per 1-mmol increase in magnesium.*

An “unknown factor” might exist, however, that causes both ECG changes and a decrease in serum magnesium. Adjustment for this unknown factor would then markedly influence the relation between serum magnesium and ECG changes. Possible candidates for this are free fatty acids,30 catecholamines, and sympathetic stimulation.31 The decrease in serum magnesium and thus the increase in intracellular magnesium then have only an attenuating effect. Another candidate for this unknown factor is coronary vasospasm.32 This does not rule out a mediating role of magnesium because decreasing the serum magnesium causes vasospasm.33

Another possibility is that there is a U-shaped relation between serum magnesium and QTc interval. Both hypermagnesemia and hypomagnesemia result in prolongation of the interval, as is often the case in electrolyte disturbances. Although the data for hypermagnesemia are lacking in this study, we do not find support for this theory because the QTc interval is especially prolonged in the normal serum magnesium range and normal in the hypomagnesemia range.

The third possibility is that there is a delay in the shift of magnesium from extracellular to intracellular. The initial decline in serum magnesium yields the ECG changes, later corrected by the intracellular rise in magnesium levels. That could explain why there is an initial prolongation of the QTc interval after SAH that is relatively less pronounced in the presence of hypomagnesemia and thus intracellular hypermagnesemia.

From the results of this study, we think that the third option is a plausible explanation. To clarify this relation between extracellular and intracellular magnesium and ECG abnormalities, we have to look at the biochemical background. The QT interval represents the total duration of the depolarization and repolarization phases of the myocardium. The QT interval can be prolonged by a slower inactivation of inward depolarizing sodium currents, enhancing inward calcium currents, or by slower outward repolarizing potassium currents.34,35 Magnesium regulates several cardiac ion channels, including the calcium channel and outward potassium currents, through the delayed rectifier.36 Lowering the cytosolic magnesium concentration by magnesium depletion will markedly increase these outward currents, shortening the action potential and increasing susceptibility to dysrhythmias.

Intravenous magnesium is regarded as the treatment of choice for immediate treatment of torsade de pointes associated with the long QT syndrome, regardless of the serum magnesium level.37 How magnesium prevents the recurrence of torsade de pointes is not clear, but its effect may be mediated by blocking of sodium or calcium currents.38 Magnesium therapy does not affect the duration of the QTc interval, but it results in a stronger correlation between QT and RR intervals and stabilizes cardiac repolarization.39

The sarcolemmal calcium, potassium, and chloride currents are significantly modulated by magnesium, and a reduction in intracellular free magnesium contributes to a prolonged repolarization.40,41 Increased cytosolic magnesium shortens the action potential,40 probably because of a doubling of peak calcium currents.36 Because intracellular magnesium is increased after SAH as a result of the influx from serum magnesium, this may extend the action potential and
explain the relation found in our study between a decrease in serum magnesium and thus an increase in cytosolic magnesium and diminished prolongation of the QTc interval.

**PR Interval**

Although the presence of a prolonged PR interval was not frequent in our study, we found a strong relation between decreased serum magnesium and prolongation of the PR interval. Prolongation of the PR interval is one of the known clinical manifestations of hypomagnesemia, but it has also been described with the existence of hypermagnesemia. Moreover, there is convincing evidence that magnesium infusion is slowing conduction through the atrioventricular node and thus prolongs the PR interval.

The relation between low serum magnesium and prolongation of the PR interval might be caused by the same mechanism as the relation between low serum magnesium and QTc prolongation: Decreased serum magnesium levels after SAH are followed by increased cytosolic magnesium and consequent prolongation of the PR interval.

**QRS Complex**

The duration of the QRS complex in our study population was longer than could be expected in a normal population. Widening of the QRS complex has been described with even modest magnesium loss but also with hypermagnesemia. The effect of magnesium therapy on the QRS complex is not consistent, but mostly a widening of the QRS complex has been reported. In our study, we found a nonsignificant relation between widening of the QRS complex and a decrease in serum magnesium.

**Conclusions**

In this study, we confirmed that patients with SAH often have a long QTc interval and low serum magnesium. In patients with SAH, lower serum magnesium concentrations are associated with less prolonged QTc intervals. From these results, we hypothesize that the decrease in serum magnesium after SAH, because of intracellular shift, causes changes in the PR and QTc intervals and may provoke U-wave abnormalities. The following increase in cytosolic magnesium has an opposite effect on the PR and QTc intervals and may explain why low serum magnesium is related to a less pronounced prolongation of the QTc interval and prolongation of the PR interval. The fact that ECG changes appear mainly in the first 72 hours after SAH, as does hypomagnesemia, strengthens this hypothesis. Our advice for clinical practice in patients with ECG changes after SAH is to measure serum magnesium. Magnesium therapy might be worthwhile and should be the focus of further study.

**Acknowledgments**

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**References**


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