Red Cell Magnesium Concentration in Cor Pulmonale*

Correlation With Cardiopulmonary Findings

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Atomic absorption spectrometry was used for red cell (MgRC) and plasma Mg (MgPL) measurement (mEq/L) in 24 normal individuals (Nls), aged 42.16 ± 16 years, and 44 carefully selected consecutive patients (pts), aged 60.68 ± 10 years with cor pulmonale. The results showed the following: (1) normal MgPL (1.69 ± 0.19) and MgRC (4.22 ± 0.32) in Nls; (2) decreased MgPL (1.56 ± 0.23) and MgRC (2.85 ± 0.54) in pts; (3) decreased FEV, percent (37.56 ± 13.1) in pts; (4) increased RVIDd (1.73 ± 0.31 cm/ml) of the pts by M-mode echo; and (5) coexistence of decreased MgRC (2.55 ± 0.33) and ECG arrhythmias-RBBB in 17/44 Pts (38.6 percent). We conclude the following: (1) red cell Mg concentration was more significantly decreased (p<0.001) than plasma Mg concentration (p<0.01); (2) there was no significant correlation coefficient (r) between red cell and plasma Mg concentration of pts (p>0.05); (3) there was significant statistical difference between decreased red cell Mg levels in pts with and without ECG arrhythmias-RBBB (p<0.01); (4) significant r between decreased red cell Mg concentration and RVIDd (r = −0.43, p<0.01), β FEV, percent (r = 0.47, p<0.01); and (5) decreased red cell Mg levels of unknown origin have never been reported previously in the literature. Subsequently, could Mg salt intake attenuate pulmonary dysfunction and right ventricular dilatation in pts with chronic cor pulmonale?

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CP = cor pulmonale; CPD = chronic pulmonary disease; IVStd = interventricular septal thickness in diastole; Mg = magnesium; MgPL = plasma magnesium; MgRC = red cell magnesium; Nls = normal individuals; RBBB = right bundle branch block; RVH = right ventricular hypertrophy; RVIDd = right ventricular internal diameter in diastole; RVWTd = right ventricular wall thickness in diastole.

Magnesium is the second most abundant intracellular cation in the body,1 next to potassium, while less than 1 percent of the total body magnesium is found in the extracellular compartment. Thus, plasma levels alone may not reflect tissue levels, which explains why the plasma magnesium level is not indicative of the intracellular magnesium content. Thus, the physician should always measure the magnesium content of blood cells (erythrocytes, lymphocytes) or the skeletal muscle cells.2 Many studies suggest an important role of magnesium in various clinical syndromes and diseases, like hypokalemia and hypocalcemia, respiratory muscle weakness, cardiac arrhythmias, arterial hypertension, or ischemic heart disease.3 On the other hand, magnesium deficits have been reported in many disorders,4,5 accompanied by a variety of structural and functional disturbances6,7 or may occur as a consequence of drug therapy, such as after aminoglycosides8 and digoxin9 therapy.

Despite the known frequency of this metabolic disorder, little is known about the prevalence and clinical implications of hypomagnesemia in patients with chronic pulmonary disease and chronic cor pulmonale. This study aims to evaluate red cell and plasma Mg levels as well as its correlation with cardiopulmonary examinations in patients with cor pulmonale, which, to the best of our knowledge, has never been reported in the literature.

MATERIALS AND METHODS

Subjects

Forty-four carefully selected consecutive patients, aged 60.68 ± 10 years, admitted to the Aristotle University Cardiopulmonary Unit of the General Hospital "George Papanikolaou," were studied. All patients had long-term pulmonary disease and concomitant cor pulmonale (Table 1). None of the patients was known to have hypomagnesemia or hypermagnesemia before hospital admission.

Design of Study

The following protocol was kept for all patients entering the study: demographic data (age, sex, and race), medication administered, and medical history were recorded. Patients with pulmonary disease exacerbation or right-sided heart failure were excluded from the study. All patients studied were free of known medication causing renal loss of Mg10 for at least three days prior to hospital admission.

Table 1—Pulmonary Diseases of Patients Studied

<table>
<thead>
<tr>
<th>Pulmonary Disease</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pulmonary disease</td>
<td>13</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary emphysema</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>10</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonecomy</td>
<td>1</td>
</tr>
<tr>
<td>Pickwickian syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Thoracoplasty</td>
<td>3</td>
</tr>
<tr>
<td>Subtotal</td>
<td>44</td>
</tr>
</tbody>
</table>

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admission. They had no other abnormality in their history and were receiving normal dietary intake. At the time of hospital admission, a blood sample was collected for plasma and erythrocyte Mg determination, performed by atomic absorption spectrophotometry (Perkin-Elmer 303 model). The findings from other respiratory and cardiac parameters, such as forced expiratory 1-s volume (FEV$_1$), ECG (Table 2), and M-mode echocardiography (in 39/44 patients, Table 3) were also recorded.

**Definitions**

In our laboratory, atomic absorption spectrophotometry was also used for red cell and plasma magnesium measurement in 24 normal individuals (Nls), aged 42.16±16 years, who were defined as the control group. Normal plasma and red cell magnesium concentrations were found to be 1.69±0.19 mEq/L and 4.22±0.32 mEq/L, respectively. Hypomagnesemia was, therefore, defined as a plasma Mg level of 1.31 mEq/L or less and a red cell Mg level of 3.58 mEq/L or less, while hypermagnesemia was defined as a value of 2.07 mEq/L and 4.86 mEq/L or more in plasma and red cells, respectively.

**Statistical Analyses**

Data were analyzed using χ$^2$ testing (fourfold table with Yate's correction), Pearson's product correlation coefficient, and Student's $t$ testing for analysis of repetitive measurements. The difference between groups was determined by calculation of an analysis of variance (F test). The mean (±SD) was determined for variables as indicated. Significance was defined as a p value of less than 0.05. All statistical analyses were performed with personal computer (Hyundai PC, using the Microstat INC. release 4, and Harvard Graphics statistical program).

**RESULTS**

Of the 44 patients studied, red cell and plasma magnesium levels were 2.85±0.54 mEq/L and 1.56±0.23 mEq/L, respectively (Fig 1). Using Student's $t$ test, there was significant statistical difference between red cell Mg levels in patients and controls ($p<0.001$). Similarly, there was significant statistical difference between plasma magnesium levels in patients and controls ($p>0.01$). Low red cell Mg concentration (Mg<3.58 mEq/L) was found in 38/44 patients (86 percent), while low plasma Mg concentration (Mg<1.31 mEq/L) was found only in 5/44 patients (11 percent). It is important to note that low red cell Mg concentration was present in all five patients with plasma hypomagnesemia but plasma hypomagnesemia was not definitely found in those with low red cell Mg concentration. No correlation existed between red cell and plasma magnesium concentration in patients ($r=-0.09$, $p>0.05$) from simultaneously collected samples. The absence of a correlation between red cell and plasma magnesium concentration suggests the parallel measurement of Mg cations in those compartments.

All patients had chronic pulmonary disease with an FEV$_1$ percent = 37.56±13.1 of predicted. There was no significant statistical correlation between plasma magnesium levels and FEV$_1$ percent of the 44 patients studied ($r = 0.17$, $p = 0.05$); however, significant statistical correlation was found between red cell Mg levels and FEV$_1$ percent of the patients ($r = 0.47$, 0.01<p=0.001) (Fig 2). This significant correlation therefore suggests some bronchodilator action of Mg cations.

Twelve-lead ECG examination, performed in all patients (Table 2), revealed normal ECG in 8/44 patients (18.2 percent) (group 1), ECG criteria for diagnosing right ventricular hypertrophy in 29/44 patients (group 2), and ECG arrhythmias (supraventricular and ventricular extrasystoles, complete or incomplete right bundle branch block [RBBB]) in 17/44 patients (group 3). The mean plasma magnesium concentration was 1.61±0.17 mEq/L, 1.55±0.22 mEq/L, and 1.57±0.28 mEq/L in the three groups, respectively. Furthermore, mean red cell magnesium concentration was 1.73±0.31 mEq/L and 1.56±0.23 mEq/L in normal subjects and patients (mean±SD).

![Figure 1. Red cell (MgRC) and plasma (MgPL) concentration in normal subjects and patients (mean±SD).](image-url)

**Table 3—M-Mode Echocardiographic Findings in 39 Patients With Chronic Cor Pulmonale**

<table>
<thead>
<tr>
<th>M-Mode Parameters</th>
<th>Mean (± SD)</th>
</tr>
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<tbody>
<tr>
<td>RVIDd, cm/m²</td>
<td>1.73 (0.31)</td>
</tr>
<tr>
<td>RVWTd, cm</td>
<td>0.72 (0.14)</td>
</tr>
<tr>
<td>IVSTd, cm</td>
<td>1.22 (0.18)</td>
</tr>
</tbody>
</table>

*RVIDd = right ventricular internal diameter in diastole; RVWTd = right ventricular wall thickness in diastole; IVSTd = intraventricular septal thickness in diastole.*
FEV₁ = forced expiratory volume in one second
MgRC = Red cell magnesium concentration

**FIGURE 2.** Significant statistical correlation between FEV₁ percent and MgRC levels of the 44 pts.

Concentration was 3.25 ± 0.57 mEq/L, 2.78 ± 0.5 mEq/L, and 2.55 ± 0.33 mEq/L, respectively (Table 4).

There was no difference between plasma Mg concentration of patients with normal and abnormal ECG (χ² = 1.25, p > 0.1), but the same statistical analysis for erythrocytes Mg concentration between those two groups revealed significant difference (χ² = 4.72, p < 0.05). Furthermore, analysis of variance, using the

![Graph showing correlation between FEV₁ and MgRC](image)

**FIGURE 3.** Significant statistical correlation between RVIDd (M-mode echo) and MgRC of the 39 pts.

F test, performed among the three groups (Table 4), revealed significant difference for red cell Mg concentration (p < 0.01), not existing for plasma magnesium concentration (p > 0.05).

In 39 of 44 patients, the echocardiographic examination by M mode was diagnostic for right ventricular dilatation (Table 3). The imaging in five patients was impossible because of their hyperinflated lungs. The mean plasma and red cell Mg concentration of those 39 patients was 1.56 ± 0.23 mEq/L and 2.82 ± 0.52 mEq/L, respectively. No correlation existed between plasma Mg concentration and right ventricular internal diameter in diastole (RVIDd), right ventricular wall thickness in diastole (RVWTd), and intraventricular septal thickness in diastole (IVSTD) (p > 0.05) of those patients. However, there was significant correlation between red cell Mg levels and RVIDd (r = -0.43, p < 0.01) (Fig 3).

**DISCUSSION**

The high prevalence of red cell hypomagnesemia observed in the present study has never been reported previously in the literature, to our knowledge. Low

**Table 4—Analysis of Variance Between MgRC and MgPL. Values Regarding ECG Changes**

<table>
<thead>
<tr>
<th>ECG Group</th>
<th>No. of Patients</th>
<th>Mean (± SD)</th>
<th>F Test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MgRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>3.25 (0.57)</td>
<td></td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>2.78 (0.50)</td>
<td>6.12</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>2.55 (0.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MgPL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>1.61 (0.17)</td>
<td></td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>1.55 (0.22)</td>
<td>0.20</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>1.57 (0.28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*s = significant; ns = nonsignificant; MgPL = plasma magnesium concentration; MgRC = red cell magnesium concentration.
muscle and serum magnesium levels, found in pulmonary ICU patients, support our findings. Similarly, recent results presented by Dr. Hauser during the Third European Congress on Magnesium 1990 showed a statistically significant improvement in FEV1, (p<0.02) of 17 patients with confirmed bronchial asthma, treated with antiasthmatic therapy and Mg salts simultaneously; this was suggestive of the presence of hypomagnesemia. The association between intracellular hypomagnesemia and severe bronchial obstruction, therefore, suggests some bronchodilator action of magnesium cations and is, obviously, in strong relationship with Dr. Hauser’s results. This important observation, promoting new therapeutic devices, needs further investigation.

No correlation was found between plasma and red cell Mg levels in our patients. These data parallel a significant group of previous reports that suggest that intracellular and extracellular Mg concentrations can vary independently and a deficit in one may not be accompanied by a significant change in the other. Since plasma magnesium levels have been poorly correlated with tissue magnesium levels in red cells, it is essential that the measurement of both the intracellular and extracellular Mg should be determined simultaneously.

None of the known causes was an apparent precipitant for the development of hypomagnesemia in our patients; however, it is supposed that long-term therapy prior to the study, including diuretics, digoxin, \(\beta\)-stimulants, and antibiotics, which produce renal loss of Mg\(^{2+}\), stress, inadequate intake because of extreme dyspnea and perhaps, aging, may cause an intracellular shift of magnesium.

It is noticeable that no correlation was found between magnesium deficiency and clinical signs or symptoms. This is in agreement with reports of Kingston et al. and Zaloga.

We conclude that the physiologic effect of mild decreases in extracellular and the cellular effects of low intracellular magnesium concentrations require further study and understanding of Mg metabolism.

However, the relationship between intracellular hypomagnesemia and ECG arrhythmias in patients with cor pulmonale secondary to chronic pulmonary disease would appear to be an important observation. Many studies report the arrhythmogenic effect of serum Mg deficiency, and it is well known that magnesium salts are frequently used for their antiarrhythmic and neuronal effects even in normomagnesemic patients. The authors suggest that reversal with magnesium administration might indicate tissue deficiency, but this has not been rigorously tested. The presence of significant correlation between red cell magnesium concentration and ECG arrhythmias in our patients suggests a better understanding of this phenomenon.

Furthermore, we identified for the first time the association of hypomagnesemia and right ventricular dilatation by M-mode echocardiography in patients with cor pulmonale. The usefulness of M-mode evaluation of the right side of the heart is limited, particularly in patients with chronic pulmonary disease and abnormalities of thoracic configuration or hyperinflated lungs. Despite these limitations, the M-mode echocardiography provides an excellent screening test for right ventricular dysfunction by depicting chamber size and wall thickness, so that other invasive diagnostic procedures are usually unnecessary.

Very recent experimental studies in rats indicate that Mg\(^{2+}\) treatment can prevent development of experimental, chemically induced, pulmonary hypertension. These reports are in agreement with the negative correlation between intracellular Mg levels and the size of the right chamber of the heart of our patients.

We speculate that magnesium deficiency, found in patients with chronically severe airways obstruction, plays a role in the development of pulmonary hypertension and cor pulmonale. Patients with chronic pulmonary disease, right ventricular dilatation and concomitant arrhythmias-RBBB are at increased risk for hypomagnesemia and, therefore, Mg replacement therapy in association with the other medication, should not be ignored.

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14th Annual Scientific Sessions, NASPE

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