well with those by a commercial assay involving immunoinhibition of salivary amylase: \( r = 0.957 \) and 0.946 (Figure 2).

The described immunocatalytic assay of pancreatic amylase is simple to perform, gives final results within 1 h, shows good performance characteristics, and is highly specific for pancreatic amylase in samples from different types of patients.

References

**Hypomagnesemia and Low Alkaline Phosphatase Activity in Patients’ Serum after Cardiac Surgery**

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Significant decreases in magnesium (Mg) concentration and alkaline phosphatase (ALP, EC 3.1.3.1) activity in serum were seen in patients after cardiac surgery with cardiopulmonary bypass (Group 1), as compared with non-cardiac-surgery patients after general anesthesia (Group 2) or only spinal anesthesia (Group 3). Mean changes for Mg and ALP by the first postoperative day, compared with pre-operative baseline values, were as follows: Group 1: Mg -7.5 mg/L (−38.3%), ALP - 46 U/L (−48.4%); Group 2: Mg -3.3 mg/L (−17.4%), ALP - 17 U/L (−16.5%); and Group 3: Mg - 1.9 mg/L (−10.0%), ALP - 15 U/L (−14.0%). The decreases in Mg and ALP observed in post-cardiac-surgery patients appear to be a consequence of the cardiac surgery and the cardiopulmonary bypass pump. Measurement of Mg and ALP in a subgroup of 10 cardiac-surgery patients for 10 days postoperatively showed initial decreases, with gradual recovery to near-normal values by the 10th day. That the changes in Mg and ALP seen postoperatively were not attributable to hemodilution alone was confirmed by measuring total-protein concentrations before and after operation. ALP requires Mg ion in vitro for optimal activity, but addition of Mg in the appropriate amounts to sera with low ALP activity did not restore ALP activity. The low ALP activity seen in post-cardiac surgery patients in vivo may perhaps be related to factors other than Mg that were removed by the cardiopulmonary bypass pump.

**Additional Keyphrases:** magnesium · alkaline phosphatase · total protein · cardiopulmonary bypass · general and spinal anesthesia

Several investigators (1–4) have noted hypomagnesemia in patients after cardiac surgery—as have we. We have also seen significant decreases in serum alkaline phosphatase

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Received December 16, 1988; accepted January 30, 1989.
[EC 3.1.3.1; orthophosphoric-monoester phosphohydrolase (alkaline optimum); ALP] activity in them. Because these appear to be consistent findings after cardiac surgery, we undertook a study to better document the postoperative changes in magnesium and ALP activity in serum, and their persistence, in cardiac-surgery patients.

We also compared these changes observed in the cardiac-surgery patients with those for a cohort of surgical patients who were not undergoing cardiac surgery and were not placed on cardiopulmonary bypass. These control groups of surgical patients had either undergone general anesthesia for major surgery or had only spinal anesthesia for relatively minor surgical procedures.

Materials and Methods

Patient population. All surgical patients were selected without conscious bias from the operating schedule of the Brockton/West Roxbury Veterans Administration Medical Center Surgical Service, except that all three groups of 25 patients each were matched for sex and age. The patients in Group 1 were undergoing cardiac surgery, ranging from coronary artery bypass graft procedures to cardiac-valve replacement. Group 2 patients underwent general anesthesia for various surgical procedures not involving cardiopulmonary bypass or thoracic surgery; however, all of these procedures (e.g., cholecystectomy or intestinal resection) involved considerable surgical trauma. Group 3 patients had spinal anesthesia for various surgical procedures, again not involving cardiopulmonary bypass or thoracic surgery; all of these were minor surgical procedures such as transurethral prostatic resection or hernia repair.

Specimen collection. Serum was sampled from all patients for baseline pre-operative studies between 24 and 48 h before surgery. Postoperative specimens were obtained on the first postoperative day, usually between 16 to 30 h after surgery. In a subgroup of 10 randomly selected cardiac-surgery patients, serum was also sampled on postoperative days 3, 5, 7, and 10.

Measurements were usually performed on the day of collection, if possible, or specimens were stored at 4 °C and assayed (usually) within 48 to 72 h after collection.

Biochemical measurements. Serum magnesium was determined in the ao III analyzer (DuPont Co., Wilmington, DE 19898) by a modified methylthymol blue complexometric procedure. Normal reference values for magnesium were 18–24 mg/L, based on studies in the literature. ALP activity and total protein were determined with the "Astra Ideal" system (Beckman Instruments, Brea, CA 92621) according to the manufacturer's kinetic procedure and the biuret reaction, respectively. Normal reference values for ALP activity were 30–115 U/L and for total protein 60–80 g/L, based on published studies.

Results

Table 1 summarizes the data for all of the three groups. Pre- and postoperative values for each analyte as well as the mean change for Mg and ALP are shown. The largest absolute and percentage changes for Mg and ALP were seen in the cardiac-surgery patients, whose decreases in Mg and ALP were of similar magnitude (−40% and −50%, respectively). Patients in Groups 2 and 3 showed similar but less-dramatic changes in both analytes.

Figure 1 displays all the data for the three groups of surgical patients. The change in pre- vs post-surgery values for magnesium and ALP activity was greatest in the cardiac-surgery group, less in the general-anesthesia patients, and smallest for the spinal-anesthesia patients. By one-way analysis of variance (ANOVA), the difference between the pre-operative and one-day postoperative values for Mg and ALP for each of the three groups of patients was statistically significant (P < 0.001 for both Mg and ALP). By Student's t-test, there was no significant difference pre-and post-operation between Groups 2 and 3 for Mg and ALP, but there were significant differences between Group 1 and Group 2 and between Group 1 and Group 3 (P < 0.001, for all comparisons).

We also studied a subgroup of 10 cardiac-surgery patients before and on days 1, 3, 5, 7, and 10 after surgery, to evaluate the persistence of the changes in Mg and ALP. We used total-protein measurements to relate changes in each analyte to pre-operative values to minimize the hemodilution effect on each analyte. The following ratios were used:

- Total protein (TP) on given postoperative day/pre-operative TP
- Alkaline phosphatase (ALP) on given postoperative day/pre-operative ALP
- Magnesium (Mg) on given postoperative day/pre-operative Mg

Figure 2 shows the results of graphing these ratios for total protein, magnesium, and alkaline phosphatase. Paired t-tests showed that there was a statistically significant difference between ratios 1 and 3 for day 1 and also between ratios 2 and 3 for days 1 and 3; for all other days, there was no significant difference between the ratios. These results show that hemodilution alone could not account for the changes in ALP and Mg in the cardiac-surgery patients. Figure 2 illustrates the gradual recovery of Mg and ALP activity, which was almost complete by the 10th postoperative day. Total protein decreased on the first postoperative day and did not fully recover.

We attempted to determine experimentally whether the low ALP activity was related to the low Mg²⁺ concentration.

Table 1. Mg and ALP Activity Concentrations in Surgical Patients (Mean ± SD, and Range)

<table>
<thead>
<tr>
<th></th>
<th>Mg, mg/L</th>
<th></th>
<th>ALP, U/L</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-op</td>
<td>Postop day 1</td>
<td>Mean change in Mg, %</td>
<td>Pre-op</td>
</tr>
<tr>
<td>Group 1</td>
<td>19.6 ± 2.4, 15–25</td>
<td>12.1 ± 2.2, 8–15</td>
<td>−38.3</td>
<td>95 ± 29, 42–192</td>
</tr>
<tr>
<td>Group 2</td>
<td>19.0 ± 2.0, 16–23</td>
<td>15.7 ± 2.5, 11–20</td>
<td>−17.4</td>
<td>103 ± 31, 60–184</td>
</tr>
<tr>
<td>Group 3</td>
<td>19.4 ± 1.5, 17–22</td>
<td>17.5 ± 1.6, 15–20</td>
<td>−10.0</td>
<td>107 ± 59, 33–317</td>
</tr>
</tbody>
</table>

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If the ALP activity was indeed decreased because of hypomagnesemia, then the in vitro addition of Mg²⁺ in appropriate amounts should restore this enzyme’s activity. However, when sufficient Mg²⁺ was added to postoperative serum specimens with low ALP activity to increase the Mg²⁺ concentration to pre-operative levels, no change in ALP activity resulted.

Discussion

Hypomagnesemia has been observed in patients after surgery, although inconsistent changes in serum and urinary magnesium have been reported (1, 2, 5–8). Others have reported significant hypomagnesemia in patients after cardiac surgery. Scheinman et al. (4, 9) studied 12 patients who were undergoing cardiopulmonary-bypass surgery with a nonblood pump prime and showed a 30% decrease in Mg on postoperative day 1, a finding they attributed to dilution of extracellular fluid volume and renal urinary Mg excretion (4, 9). Holden et al. (3) found hypomagnesemia in patients undergoing open-heart or noncardiac (pneumonec- tomies and esophageal) surgery, noting a greater fall and persistence of hypomagnesemia postoperatively in open-heart surgery as compared with non-perfusion thoracic-surgery patients, an observation they ascribed partly to metabolic response to surgical trauma. They (3) also found correction of serum magnesium abnormalities by the time of discharge of cardiac-surgery patients (seventh postoperative day). In the pediatric age group, serum magnesium concentrations decrease rapidly after cardiopulmonary-bypass surgery (~14%) but return to pre-operative values by the third postoperative day (10).

Clinically, the low serum magnesium concentration seen in cardiac-surgery patients may result in a magnesium deficiency cardiomyopathy, reflected by increased myocardial vulnerability to arrhythmias and necrosis (11), suggesting that restoration of serum magnesium to normal may play a role in avoiding potential cardiac complications (11).

Decreased serum alkaline phosphatase activity has been observed (10) in infants who are undergoing cardiac surgery with profound hypothermia, circulatory arrest, and limited cardiopulmonary bypass. Some investigators (12) have described hypomagnesemia associated with low serum alkaline phosphatase activity in several patients with intestinal malabsorption. Others (13) have noted decreased serum alkaline phosphatase activity in cases of hypothyroidism and have speculated on the possible causative role of low serum magnesium and zinc in this phenomenon. In experimental studies, rats fed a magnesium-deficient diet for up to 34 days demonstrated depressed alkaline phosphatase activity, which was reversed by adding magnesium to the diet (12).

Magnesium ion is an important activator for the optimal enzymatic activity of serum alkaline phosphatase (14), but addition of magnesium ion in appropriate amounts in vitro to sera with low ALP activity did not restore ALP activity. We speculate that the low ALP activity observed in cardiac-surgery patients in vivo was not related to low Mg concentration but rather to factors removed by the cardiopulmonary pump.

Finally, we mention the association of low ALP activity with vitamin B₁₂ deficiency (15), a finding suggesting that vitamin B₁₂ deficiency impairs osteoblast activity and synthesis of ALP (16).

This work was supported in part by the Richard Warren Surgical Research and Educational Fund, Westwood, MA 02090.

References

Proton Nuclear Magnetic Resonance Studies of Plasma to Determine Metabolic Status of Patients with Adult Respiratory Distress Syndrome

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Adult respiratory distress syndrome (ARDS) is a non-cardiogenic pulmonary edema of various etiologies. Here we report the first application of proton nuclear magnetic resonance (NMR) for the detection of abnormal metabolites in plasma from patients with ARDS. By comparing plasma obtained from the systemic artery with that obtained from the pulmonary artery, we could study the metabolic status of the lung in patients with ARDS. Although their concentrations may vary, the peaks for acetate, acetoacetate, β-hydroxybutyrate, phenylalanine, and other unidentified compounds in water-suppressed NMR of these patients’ plasma were higher than in the normal controls. The proton NMR resonance at a chemical shift of about 7.4 ppm (relative to sodium tetradecatriene-3-trimethylsilylproponate), presumably caused by phenylalanine and its related metabolites produced by a disordered amino acid metabolism, is detected in >65% of the samples from ARDS patients. We discuss the detection of abnormal metabolites in terms of possible deranged metabolism of carbohydrates, lipids, or amino acids in this syndrome.

Additional Keyphrases: lung disease - phenylalanine

Adult respiratory distress syndrome (ARDS) is a catastrophic illness with a high mortality rate; it can be provoked by many illnesses, including sepsis of various origins, aspiration pneumonia, and bone fracture (7). Many cellular factors, such as neutrophils, and humoral factors, such as derivatives of arachidonic acid, are believed to be involved in the pathogenesis of ARDS (2). Leaks in the pulmonary endothelium and epithelium, perhaps due to metabolic changes induced by these factors, are currently believed to be the mechanism of the pathogenesis of non-cardiogenic pulmonary edema. By comparing the composition of the arterial plasma of the patients with that of normal controls, we may be able to detect abnormal metabolites in the blood of patients with ARDS. Furthermore, by comparing the composition of the arterial plasma with that of the mixed venous plasma, we may be able to distinguish the detected metabolites from xenobiotic compounds. The mixed venous plasma obtained at the same time can serve as a control in the same patient for the detection of changes in the arterial plasma.

Nuclear magnetic resonance (NMR) is well suited for non-destructive screening of biomaterials, and involves minimal sample pretreatment (3–8). However, the determinations of concentrations of metabolites by NMR are hindered by the binding of the metabolites to plasma proteins (9), variations in linewidth, and the low sensitivity of NMR in comparison with other analytical methods (e.g., HPLC and gas chromatography). Because the metabolic status of ARDS patients may vary greatly and rapidly, a quick and easy diagnostic method is required to monitor such changes. We examined water-suppressed proton NMR as a tool for screening metabolites in plasma samples from ARDS patients.

Materials and Methods

Included in this study were 17 patients diagnosed as having ARDS (of known etiologies). Both an arterial line and a Swan–Ganz catheter were inserted when the patients were first seen in the Intensive Care Unit of the Veterans General Hospital, Taipei, for the measurement of systemic arterial pressure, pulmonary capillary wedge pressure, cardiac output, and so on. From both sampling sites, we collected 10 mL of blood from each patient. After thorough mixing with heparin, the blood was centrifuged at 3000 × g for 20 min to eliminate its cellular components, and the plasma thus obtained was stored at −80 °C for later NMR studies and protein measurements. As a control, we also obtained arterial plasma from nine healthy volunteers by