Do Ionized Calcium and Phosphorus Levels have any Prognostic Value in Patients with ST-Segment Elevation Myocardial Infarction?

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Abstract

Introduction: The significance of serum calcium and phosphorus levels in patients with acute myocardial infarction is not entirely clear.

Objective: To assess the potential predictive value of ionized calcium (iCa) and phosphorus levels in acute ST-segment elevation myocardial infarction (STEMI) patients treated using primary percutaneous coronary intervention.

Design and Methods: A total of 256 patients included in the STEMI-RADIAL study were evaluated. Calcium and phosphorus levels were measured on admission, and after 6 h and 12 h. Correlations of these values with other laboratory and clinical parameters were assessed.

Results: Within the first 12 h of admission we observed a statistically significant increase in iCa and phosphorus levels; none of the patients received iCa or phosphorus supplementation. Hypocalcemia was present in 14% of patients at baseline and was associated with increased troponin I levels (P<0.0018). After adjustment for confounders, a higher left ventricular ejection fraction was associated with increased iCa levels after 12 h (P=0.010) and lower values of peak troponin I (P=0.0001) and C-reactive protein (CRP; P<0.0006) levels. Baseline hypophosphatemia was associated with longer chest pain duration (P=0.044) and lower CRP levels after 24 h (P=0.040). The mortality rate of the group after one month and one year was 1.32% and 3.08%, respectively. Of the biochemical parameters studied, only the CRP level was associated with higher one-month mortality (odds ratio [OR] 4.01 [95% confidence interval (CI) 1.16 to 13.9]; P=0.029). Twelve-month mortality was associated with CRP level (OR 2.21 [95% CI 1.00 to 4.89]; P=0.049) and also patient age (OR 1.08 [95% CI 1.00 to 1.17]; P=0.045).

Conclusion: We did not find any prognostic value with regard to baseline levels of ionized calcium and phosphorus. We observed an association between iCa levels 12 h after admission and left ventricular systolic dysfunction in STEMI patients. However, the clinical relevance of this finding is not yet clear. Patients with longer chest pain duration had lower baseline phosphorus levels.

Keywords: Ionized calcium; Left ventricular ejection fraction; Phosphorus; STEMI; Troponin I

Abbreviations

BMI: Body Mass Index; CK: Creatine Kinase; CRP: C-Reactive Protein; Ica: Ionized Calcium; IHD: Ischemic Heart Disease; LVEF: Left Ventricular Ejection Fraction; PCI: Percutaneous Coronary Intervention; STEMI: ST-Segment Elevation Myocardial Infarction

Introduction

The significance of serum calcium and phosphorus levels in relation to myocardial necrosis markers, C-reactive protein (CRP) levels, and clinical presentation in acute myocardial infarction patients has not been fully established.

Hypocalcemia (ionized Ca [iCa] ≤ 1.12 mmol/L) is a relatively common problem in critically ill patients, particularly those with sepsis, acute necrotizing pancreatitis, rhabdomyolysis, trauma, and systemic inflammatory response syndrome [1-7], and the etiology appears to be multifactorial. Data published to date suggests several different mechanisms may be involved: (i) cytokine-mediated inflammatory response [8], (ii) increased binding to proteins (albumin) [9], (iii) relative parathormone deficiency, or (iv) reduced renal hydroxylase activity [10]; however, simple changes in bone metabolism and renal excretion are not considered viable options. An alkaline change acid-base balance is also a significant and well-known mechanism that can lead to hypocalcemia. Alkalosis induces hypocalcemia by promoting increased calcium binding to proteins. It has been reported that each 0.1 unit increase in pH leads to a decrease in iCa by approximately 0.05 mmol/L [11]. 'Significant' fluid replacement (especially Ca-free fluids) can also lead to dilutional hypocalcemia. It is also known that calcium supplementation, in
critically ill patients with reduced calcium levels, has been shown to increase systolic blood pressure and stroke volume [12].

Phosphorus metabolism is closely associated with calcium metabolism. Plasma phosphorus levels are also affected by pH, and alkalosis supports cellular uptake of phosphorus. Hypophosphatemia is classified as moderate (0.3 mmol/L to 0.7 mmol/L) or severe (<0.3 mmol/L). In critically ill patients, significant hypophosphatemia may contribute to rhabdomyolysis and leukocyte dysfunction as well as respiratory and heart failure [13-16]. Severe hypophosphatemia is typically observed in alcoholic patients, septic patients and patients with malnutrition or diabetic ketoacidosis, and is associated with an increased mortality risk [17,18]. Hypophosphatemia in patients with acute myocardial infarction may be caused by a stress response that requires addition energy and involves the transfer of phosphorus into cardio-myocytes, where it is transformed into adenosine triphosphate, which binds to the damaged cellular membranes of necrotic myocytes. Increased serum catecholamine levels or metabolic dysfunction can also lead to increased phosphorus loss in the urine, which can lead to or contribute to hypophosphatemia [14,19]. A positive association between increased phosphorus levels and the severity of coronary angiography findings in patients with chronic ischemic heart disease, as well as risk of death, has been found in previous studies [20,21]. In our pilot study, hypophosphatemia was present more frequently in STEMI patients than in the control group, which was comprised of patients without acute coronary syndrome [22].

The objective of the present study was to establish calcium and phosphorus levels in the acute phase of STEMI, and to assess a possible association with laboratory markers of myocardial necrosis.

Material and Methods

Study population

The present study was a prespecified laboratory substudy of the multicenter randomized STEMI-RADIAL (ST-Elevation Myocardial Infarction treated by RADIAL or femoral approach) study [23]. The STEMI-RADIAL study compared radial and femoral PCI approaches in patients presenting, within 12 h of symptom onset, with an ST-elevation myocardial infarction (STEMI), who were then treated using primary percutaneous coronary intervention (PCI) performed by experienced surgeons familiar with both access sites. Neither calcium nor phosphorus was administered during the study period.

| Age, years | 61.20 ± 10.54 |
| Male sex, n (%) | 197 (77) |
| Body mass index, kg/m² | 28.31 ± 4.10 |
| Hypertension, n (%) | 153 (60) |
| Dyslipidemia, n (%) | 95 (37) |
| Diabetes mellitus, n (%) | 46 (18) |
| Current smoker, n (%) | 158 (62) |
| Previous MI, n (%) | 28 (11) |
| Previous stroke, n (%) | 8 (3) |
| Symptoms to balloon, min | 205 (148-285) |

Table 1: Basic characteristics of the study participants (n=256). Data presented as mean ± standard deviation or median (interquartile range), unless otherwise indicated. MI: Myocardial Infarction.

The present substudy included 286 patients in one (Pilsen, Czech Republic) of four participating centres (patients were enrolled between October 2009 and February 2012). Six patients with normal coronary angiography findings and 24 patients with incomplete laboratory results were excluded; thus, a total of 256 patients were included in the final evaluation. The relationships among left ventricular ejection fraction (LVEF) and various laboratory parameters were assessed in 228 patients (28 patients with a history of ischemic heart disease were excluded from echocardiography analysis). The study was approved by the local ethics committee. Written informed consent was obtained in the catheterization laboratory immediately before the invasive procedure.

Laboratory

Levels of phosphorus and iCa were measured before coronary angiography, and 6 h and 12 h after the procedure. Acid-base values were measured on admission and after 12 h. Troponin I and creatine kinase (CK) levels were measured on admission and after 6 h and 12 h; baseline and peak values are presented in Table 3 and 4. Myoglobin and lactate levels were determined at baseline. CRP levels were evaluated in blood samples obtained 24 h after admission. Cardiac troponin I was determined using a chemiluminescent assay kit (STAT Troponin I; Abbott Laboratories Chicago, Illinois, USA) on an Architect i-2000 immunoassay analyzer (Abbott).

Levels of CK, total calcium, inorganic phosphorus, myoglobin, and CRP were measured using an Olympus AU 400 (Beckman Coulter, Princeton, New Jersey, USA). Levels of iCa, lactate and pH were measured using a blood gas analyser (Radiometer, ABL 800, Copenhagen, Denmark). For the study, reference ranges were set as 2.2 mmol/L to 2.6 mmol/L for total calcium, 1.13 mmol/L to 1.32 mmol/L for iCa and 0.7 mmol/L to 1.6 mmol/L for phosphorus.

Echocardiography was performed four to seven days after the STEMI event.

Statistical analysis

SAS version 9.3 software (SAS Institute Inc., Cary, North Carolina, USA) was used to perform all statistical analyses. The characteristics of the study population and laboratory parameters are presented as mean ± standard deviation, median and interquartile range, or as a percentage. We compared means and proportions using a standard paired Student’s t test, Kruskal-Wallis test and Fisher’s exact test, respectively. To perform regression analysis, variables with distributions skewed to the right were normalized using logarithmic transformation. We performed single and stepwise linear (left ventricular ejection fraction, CRP) and stepwise logistic (mortality) regression to identify correlates of the outcome variables. In further
analyses we investigated whether the change in iCa levels over time might be associated with LVEF.

Results

The basic characteristics of the study group, existing comorbidities, location of the infarction and time from the onset of chest pain to the opening of the coronary artery are presented in Table 1. There was a statistically significant increase in iCa (P=0.0009) and phosphorus levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that there was no calcium or phosphorus supplementation (Table 2)). It should be noted that pH levels (P<0.0001) after 6 h and 12 h (recall that...
Discussion

In our study involving STEMI patients treated using primary PCI we found a statistically significant increase in iCa and phosphorus levels during the first 12 h of hospitalization. Patients with baseline hypocalcemia had higher baseline troponin I levels, but we did not observe a correlation with peak troponin I levels or LVEF and baseline iCa. A statistically significant association between iCa levels and LVEF was found 12 h after admission. However, the clinical relevance of this association is not yet clear.

Table 4: Characteristics of the group relative to baseline phosphorus levels. Bolded values indicate statistical significance. CRP: C-Reactive Protein; LVEF: Left Ventricular Ejection Fraction; Tnl: Troponin I.

|                            | Baseline P<0.7 mmol/L (n=76) | Baseline P ≥ 0.7 mmol/L (n=180) | P    |
|-----------------------------|-------------------------------|----------------------------------|------|
| Age, years                  | 58.9 ± 11.2                   | 62.0 ± 10.6                      | 0.036 |
| CRP after 24 h, mg/L        | 7.5 (3.0-14.0)                | 10 (4-23)                        | 0.04  |
| Symptoms to balloon, min    | 232 (161-310)                 | 199 (145-273)                    | 0.044 |
| Baseline Tnl, μg/L          | 0.14 (0.06-1.36)              | 0.30 (0.05-2.04)                 | 0.25  |
| Peak Tnl, μg/L              | 60.3 (17.0-117.9)             | 71.0 (20.1-126.8)                | 0.59  |
| Lactate, mmol/L             | 1.8 (1.3-2.6)                 | 1.7 (1.3-2.4)                    | 0.37  |
| LVEF, %                     | 48.9 ± 9.4                    | 48.1 ± 9.9                      | 0.62  |
| Baseline creatinine, μmol/L | 97.0 (85.5-110.0)             | 96.5 (86.5-106.5)                | 0.76  |
| One month mortality, n (%)  | 1 (1.3)                       | 3 (1.7)                          | 0.99  |
| Twelve-month Mortality, n (%)| 1 (1.3)                       | 8 (4.4)                          | 0.29  |

Table 5: Determinants of left ventricular ejection fraction. β=Regression coefficient; iCa: Ionized Calcium; SE: Standard Error.

|                             | β ± SE     | P            |
|-----------------------------|------------|--------------|
| Peak troponin I, μg/L       | -3.30 ± 0.40 | <0.0001      |
| iCa after 12 h, mmol/L      | 18.82 ± 9.09 | 0.039        |
| C-reactive protein, mg/L    | -0.98 ± 0.51 | 0.054        |
| Body mass index, kg/m²      | 0.30 ± 0.14  | 0.033        |

While not numerous, there have been other studies that monitored phosphorus levels in myocardial infarction patients. Gould et al. [28] described a significant drop in phosphorus levels on the third and fourth post-infarction days compared with a control group. In contrast, the difference between the groups on the first day of hospitalization was not significant. Ognibene et al. [29] found a positive association between reduced phosphorus and bicarbonate levels in relation to the incidence of coronary arrhythmia in myocardial infarction patients. In 2000, while monitoring phosphorus levels in acute myocardial infarction patients, Vaidyanathan et al. [30] found an association between hypophosphatemia and left ventricular systolic dysfunction as well as 30-day mortality. In our study however, left ventricular systolic dysfunction, after 12 h, was associated with decreased iCa levels but not decreased phosphorus levels.

Acetylsalicylic acid administered in the early phase of acute coronary syndrome has a protective impact on myocardial high-energy phosphates during ischemia and reperfusion [28] and indirectly reduces phosphatemia by inducing respiratory alkalosis [31,32]. In our study, all patients were given dual antiplatelet therapy before the baseline sample was obtained, which may have had an impact on phosphatemia.

Conclusion

Baseline hypocalcemia in STEMI patients treated with primary PCI was associated with higher baseline, but not peak, troponin I levels. It was also observed that hypocalcemia 12 hours after admission was associated with left ventricular systolic dysfunction. Additionally, lower baseline phosphorus levels were observed in patients with longer...
chest pain duration. Further studies are needed to elucidate role of ionized calcium and phosphorus in STEMI patients.

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