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Original Article

Serum phosphate levels reflect responses to cardiac resynchronization therapy in chronic heart failure patients

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ABSTRACT

Background: Recent studies have shown that high levels of serum phosphate are associated with adverse cardiovascular events. However, little is known about the relation between phosphate levels and improvement of cardiac function in chronic heart failure (CHF) patients who underwent cardiac resynchronization therapy (CRT). The purpose of this study was to examine whether serum phosphate levels were able to predict responders to CRT and adverse cardiac events.

Methods: The study population consisted of 30 CHF patients (24 males, mean age 65.7 ± 8.5 years) who received CRT with defibrillator (CRT-D) implantation. Levels of serum phosphate were measured before, and 6 months after, CRT-D implantation. Left ventricular end-diastolic volume and end-systolic volume were assessed simultaneously by echocardiography. In addition, the rate of re-hospitalization due to worsening of heart failure was investigated. All patients were divided into 2 groups: responders (Group-R, $n=18$) and non-responders (Group-NR, $n=12$) to CRT-D. Responders were defined as patients who showed $>15\%$ reduction in left ventricular end-systolic volume. We compared these parameters between the 2 groups.

Results: Serum phosphate levels were significantly lower in Group-R than in Group-NR (3.3 ± 0.2 vs. 3.7 ± 0.4 mg/dL, $p=0.01$). The rate of re-hospitalization was lower in Group-R than in Group-NR (0% vs. 33%, $p=0.018$). Multivariate analysis showed that serum phosphate levels had a predictive power to determine responders to CRT (odds ratio 0.008, 95% confidence interval 0.000–0.348, $p=0.015$).

Conclusions: These results suggest that serum phosphate levels might predict both responders to CRT, and adverse cardiac events, in CHF patients with CRT-D.

1. Introduction

In clinical practice, quantification of serum phosphate levels is useful for the diagnosis and management of various disorders including bone, parathyroid, and renal diseases [1]. In addition, recent studies have shown that high levels of serum phosphate, even within the normal range, may contribute to the increased risk of cardiovascular disease such as myocardial infarction and heart failure [2–4]. Interestingly, Ess et al. have reported that the association of serum phosphate concentrations with disease severity and long-term outcome in patients with chronic heart failure (CHF) is independent from concomitant renal dysfunction [4]. Their data suggest that management focused on serum phosphate levels might be important for patients with CHF.

Cardiac resynchronization therapy (CRT) is an effective treatment for drug-refractory severe heart failure with electro-mechanical delay. Previous studies have demonstrated that CRT improves clinical symptoms, exercise capacity, quality of life, and mortality in CHF [5–7]. However, responses to CRT have not been assured in all CHF patients, with about 30% of patients not responding to CRT [8].

Therefore, the aim of this study was to evaluate whether the serum phosphate levels before CRT implantation were able to predict responders to CRT, as well as adverse cardiac events. For this purpose, we examined the relation between serum phosphate levels and clinical, laboratory, and echocardiographic findings in CHF patients with CRT implantation.

2. Material and methods

2.1. Study population and protocol

The study population consisted of 30 CHF patients (24 males, mean age 65.7 ± 8.5 years) who had received successive CRT with

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defibrillator (CRT-D) implantation at Fukushima Medical University Hospital, Fukushima, Japan. Eligibility criteria for CRT were New York Heart Association (NYHA) class III/IV symptoms of heart failure despite receiving optimal medical therapy, left ventricular ejection fraction (LVEF) of 35% or less on echocardiography, and a QRS duration of 120 ms or more. The exclusion criteria were acute coronary syndrome within 6 months, chronic obstructive pulmonary disease, and hemodialysis treatment. Clinical status was evaluated before CRT-D implantation. Assessments included history of hypertension, diabetes mellitus, ischemic etiology, atrial fibrillation, present medications such as beta-blockers, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, diuretics, spironolactones, statins, and amiodarone. Patients were followed-up in our hospital for 6 months after discharge, and extensively evaluated before, and 6 months after, CRT-D implantation. NYHA classification, QRS duration, laboratory data, and echocardiographic findings were assessed. In addition, adverse cardiac events (defined as re-hospitalization due to worsening of heart failure within 6 months after CRT-D implantation), were investigated. All patients were divided into 2 groups: responders to CRT-D (Group-R, $n=18$) and non-responders to CRT-D (Group-NR, $n=12$). Responders were defined as patients who showed $>15\%$ reduction in left ventricular end-systolic volume (LVESV). Written informed consent was obtained from all study subjects. The study protocol was approved by the Ethical Committee of Fukushima Medical University (approval number, 823; approval date, March 23, 2012).

2.2. Blood sample analysis

Blood samples were collected from all patients before CRT-D implantation, in stable states of heart failure, and at 6 months after CRT-D implantation. We measured levels of serum phosphate, serum creatinine, serum calcium, high-sensitivity C-reactive protein (hs-CRP), hemoglobin, and brain natriuretic peptide (BNP). Estimated glomerular filtration rate (eGFR) was calculated by using the Modification of Diet in Renal Disease equation in keeping with the criteria of the 2002 Kidney Disease Outcome Quality Initiative guidelines [9].

2.3. Echocardiographic analysis

Transthoracic echocardiography was performed at baseline and 6 months after CRT-D implantation. Left ventricular end-diastolic volume (LVEDV), LVESV, and LVEF were assessed by the modified biplane Simpson's methods.

2.4. CRT-D implantation

CRT-D implantation was performed during compensated heart failure. The left ventricular lead was inserted through the coronary sinus with the help of a guiding catheter, and implanted at the lateral or postero-lateral vein. The right ventricular lead was positioned in the apex or septal of the right ventricular wall. All leads were inserted transvenously via the subclavian or cephalic vein route. The atrio-ventricular and inter-ventricular pacing delay was optimized by echocardiography to obtain the longest filling time or symmetrical wall motion after CRT-D implantation.

2.5. Statistical analysis

Data are reported as means $\pm$ SD, and skewed data are presented as median (inter-quartile range). Comparisons between Group-R and Group-NR were performed by using a Mann–Whitney *U* test. Data before and at 6 months after CRT-D implantation were compared by using a paired *t*-test. Categorical variables were analyzed by using a chi-square test. Multivariate logistic regression analysis was used to identify the predictors for CRT responders. The variables selected for multivariate analysis were those with $p<0.2$ in the univariate models. All analyses were performed with SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL). A p value <0.05 was considered statistically significant.

3. Results

Baseline characteristics of 30 patients are displayed in Table 1. The underlying etiologies of heart failure were ischemic in 23.3% of patients, and non-ischemic in 76.7% of patients. The non-ischemic etiology consisted of dilated cardiomyopathy in 78.3%, hypertensive heart disease in 8.7%, valvular heart disease in 8.7%, and hypertrophic cardiomyopathy in 4.3% of patients. Most of the patients received optimal medical treatment. Serum phosphate level was significantly lower in Group-R than in Group-NR (3.3 ± 0.2 vs. 3.7 ± 0.4 mg/dL, $p=0.01$). Except for the serum phosphate level, there were no differences in basic characteristics between the 2 groups (Table 2).

Table 3 shows the changes in clinical and functional parameters before and 6 months after CRT-D implantation. NYHA classification as well as serum level of BNP improved in Group-R (NYHA: 3.1 ± 0.5 to 2.4 ± 0.5, $p<0.001$; BNP: 437.2 (589.5) to 137.5 (250.8) pg/mL, $p=0.01$). In addition, LVEDV, LVESV, and LVEF improved in

Table 1
Baseline characteristics of study subjects.

Age (years)	65.7 ± 8.5
Male (%)	24 (80.0%)
Height (cm)	160.2 ± 8.9
Body weight (kg)	58.9 ± 11.5
BMI (kg/m^2)	22.8 ± 3.8
NYHA	3.2 ± 0.6
Medical history	
Hypertension (%)	11 (36.7%)
Diabetes (%)	9 (30.0%)
Hyperuricemia (%)	9 (30.0%)
Ischemic (%)	7 (23.3%)
Atrial fibrillation (%)	4 (13.3%)
Medication	
β-blocker (%)	30 (100%)
ACEI/ARB (%)	26 (86.7%)
Diuretic (%)	28 (93.3%)
Spironolactone (%)	15 (50.0%)
Statin (%)	15 (50.0%)
Amiodarone (%)	17 (56.7%)
Blood examination	
eGFR (mL/min/1.73 m^2)	53.0 ± 17.1
Phosphate (mg/dL)	3.5 ± 0.3
Calcium (mg/dL)	9.1 ± 0.50
Hs-CRP (mg/dL)	0.09 (0.11)
Hemoglobin (g/dL)	12.8 ± 2.1
BNP (pg/mL)	287.0 (418.0)
ECG	
QRS duration (ms)	159.4 ± 28.7
Echocardiography	
LVEDV (mL)	174.4 ± 71.4
LVESV (mL)	124.2 ± 60.0
LVEF (%)	28.3 ± 8.4

BMI, body mass index; NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; BNP, brain natriuretic peptide; ECG, electrocardiography; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.