ORIGINAL ARTICLE

Abnormal serum calcium levels are associated with clinical response to maximization of heart failure therapy

Piotr Rozentryt[1], Jacek T. Niedziela[1], Bartosz Hudzik[1], Wolfram Doehner[2], Ewa A. Jankowska[3], Jolanta Nowak[1], Stephan von Haehling[4], Krzysztof Myrda[1], Stefan D. Anker[4], Piotr Ponikowski[3], Lech Poloński[1]

1 Third Department of Cardiology, Silesian Centre for Heart Diseases, Medical University of Silesia, Zabrze, Poland
2 Centre for Stroke Research Berlin, Charité Medical School, Berlin, Germany
3 Department of Heart Diseases, Wroclaw Medical University, Wrocław, Poland
4 Applied Cachexia Research, Department of Cardiology, Charité Medical School, Campus Virchow-Klinikum, Berlin, Germany

KEY WORDS

abnormal calcium levels, heart failure severity, epidemiology, mortality, response to therapy

ABSTRACT

INTRODUCTION Abnormal serum calcium levels are associated with adverse cardiovascular effects. Therapy of heart failure (HF) may result in urinary calcium excretion and calcium apposition to bones, and consequently, in calcemia.

OBJECTIVES The aim of the study was to assess the prevalence of abnormal calcium levels in the blood of patients receiving maximized HF therapy, to explore clinical and laboratory determinants of abnormal serum calcium levels, and to analyze the relation of abnormal calcium levels to prognosis.

PATIENTS AND METHODS The study included 722 patients with HF classified as New York Heart Association (NYHA) classes III–IV at baseline (age 53 ±10 years, 13% of women), who underwent HF therapy optimization to maximum tolerated doses.

RESULTS After therapy maximization, the NYHA class improved in 66.7% of the patients, while it did not change in 31.0% and worsened in 2.4%. Hypocalcemia occurred in 166 patients (22.9%) and was more prevalent in patients in whom the NYHA class improved. Hypercalcemia was diagnosed in 63 patients (8.7%) and was more common in patients with no functional improvement or worsening of the NYHA class. This effect was independent of age, sex, etiology of HF, body mass index, kidney function, or the use of thiazides. Hypercalcemia was associated with increased catabolism, hemodynamic compromise, more intensive inflammation, and lower bone mineral density. Lower albumin and higher phosphorus levels, were significant predictors of hypercalcemia, independently of kidney function. Hypocalcemia was associated with reduced catabolism, higher albumin and lower phosphorus levels, use of thiazides, and smoking history. Neither hypocalcemia nor hypercalcemia was associated with poor prognosis.

CONCLUSIONS Our study shows that abnormal serum calcium levels are associated with a clinical response to treatment maximization in patients with HF. Mild hypocalcemia after maximization of therapy is not associated with poorer prognosis. Hypercalcemia is associated with lack of response to treatment, and its prognostic value remains unclear.

Correspondence to:
Piotr Rozentryt, MD, PhD, III Katedra i Kliniczny Oddział Kardiologii, Śląskie Centrum Chorób Serca, Śląski Uniwersytet Medyczny, ul. M. Curie-Skłodowskiej 9, 41-800 Zabrze, Poland, phone: +48-32-278-15-92, fax: +48-32-273-26-79, e-mail: p.rozentryt@sccs.pl
Conflict of interest: none declared.
Received: November 11, 2014.
Revision accepted: January 2, 2015.
Published online: January 12, 2015.
Pol Arch Med Wewn. 2015; 125 (1-2): 54-64

INTRODUCTION There is an increasing recognition of the role of extracellular calcium signaling for organ functioning and survival.[1] The activation of calcium-sensing receptors is implicated in the regulation of myocytes as well as endothelial, epithelial, and juxtaglomerular cells in the kidney.[2] All of these cells are important for cardiovascular function.

Heart failure (HF) is a complex clinical syndrome of increasing clinical importance,[3] in which the hyperadrenergic state, inflammation, and various metabolic derangements lead to accelerated

catabolism, weight loss, progressive multiorgan damage, and poor outcome.[4] During the hyperadrenergic state, the calcium influx into cells is driven by catecholamines, aldosterone, and parathormone excess causing organellar dysfunction on one hand, and serum ionized hypocalcemia on the other.[5] The presence of hypocalcemia in acute hyperadrenergic conditions is a prognostically ominous sign,[6] while its correction with intravenous calcium was shown to be ineffective or even harmful.[6,7]

According to the current guidelines, the hyperadrenergic state in HF should be inhibited by means of angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, and aldosterone antagonists.[8] These drugs have anticatabolic effects, and thereby may influence serum calcium levels.

Both low and high serum calcium levels were shown to be risk factors for the development or aggravation of preexisting HF and to contribute to high cardiovascular mortality.[9,10] In everyday practice, HF patients usually receive ACEIs, β-blockers, and aldosterone antagonists without the measurement of baseline calcium levels. The effect of maximizing HF therapy on serum calcium levels remains unknown, and the published guidelines do not recommend any specific therapy in patients with abnormal levels observed during escalation of HF therapy. An association between abnormal serum calcium levels during therapy maximization and clinical outcome has not been investigated so far. Therefore, we sought to examine the prevalence of abnormal serum calcium levels in patients who responded differently to the intensification of HF therapy. We also tried to identify independent clinical and laboratory predictors of calcium abnormalities. Finally, we assessed whether serum calcium abnormalities were independently associated with prognosis.

PATIENTS AND METHODS

Study group

We retrospectively reviewed outpatient charts of patients with HF who were included in the Prospective Registry of Heart Failure started in 2003 at our department and in the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF).[11] For the purpose of the current study, we selected patients with HF and reduced left ventricular ejection fraction (LVEF ≤40%), diagnosed according to the European Society of Cardiology criteria, aged 18 years or older, and with HF lasting more than 6 months. We included patients naive to a recommended therapy or receiving less than 10% of the recommended doses of ACEIs and β-blockers. Their NYHA functional class before the maximization of HF therapy had to be III or IV. Within the next 3 months, the therapy was escalated on consecutive 3 to 5 outpatient visits and finally reached the maximum tolerated doses, defined as the highest doses freeing the patient from such symptoms as hypotonia, bradycardia (<50 bpm), serum potassium levels exceeding 5.5 mmol/l or the target doses recommended by contemporary guidelines. We included patients in whom the doses of ACEIs or β-blockers had to be at least doubled, or the doses of aldosterone antagonists had to be tripled in case of an increase in an ACEI or β-blocker dose lower than double dosage. A duration of this optimal therapy had to be at least 1 month before the inclusion into the study. We excluded patients treated with glucocorticosteroids, bisphosphonates, vitamin D preparations, calcium or phosphorus salts, and those having active infection, liver disease with enzymes exceeding the upper limit of normal more than 4 times, active bleeding, known neoplasms or granulomatous disease as well as patients who underwent surgery reducing gut absorptive capacity. Patients who were included into the study had to be clinically compensated with no signs or symptoms of fluid retention. A total of 722 patients (of 1029 participants in the Prospective HF Registry or SICA-HF) met the inclusion criteria and entered the final analysis.

Based on a medical history and available patient records, we established the date of HF onset with a precision of 1 month. The highest body weight within a year before HF development and the lowest edema-free weight after HF development were considered as preHF (maximum) and minHF (minimum) body weight, respectively.

Comorbidities such as hypertension, diabetes mellitus, and hypercholesterolemia were recognized based on a clinical history, current use of medications, or actual measurements of the respective variables. Smoking history was defined as the current or previous use of tobacco products.

Blood samples were obtained using standard methods in the morning, between 8 and 10 AM, after at least 8 hours of fasting and 30 minutes of rest in the supine position in a quiet, environmentally controlled room. The blood was immediately centrifuged at a temperature of 4°C and stored at –75°C for further analyses. Fasting urine samples were also collected in the morning and stored. All procedures were conducted in accordance with the Helsinki Declaration, and the protocol was reviewed and accepted by the Ethical Committee of the Medical University of Silesia. All patients gave their written informed consent to participate in the study. The study procedures are shown in FIGURE 1.

Measurements

Body mass and height were measured at the day of inclusion into the study and blood sampling (index date) using the certified scale (B150L, Redwag, Zawiercie, Poland). All weights, that is, the maximum body weight before HF, minimum weight during HF, and the baseline weight were indexed to height and expressed as body mass indexes abbreviated as preHF BMI, minHF BMI, and baseline BMI, respectively. We calculated weight loss and weight gain using the following formulas:

weight loss (%) = 100 × (preHF BMI – baseline BMI) / preHF BMI

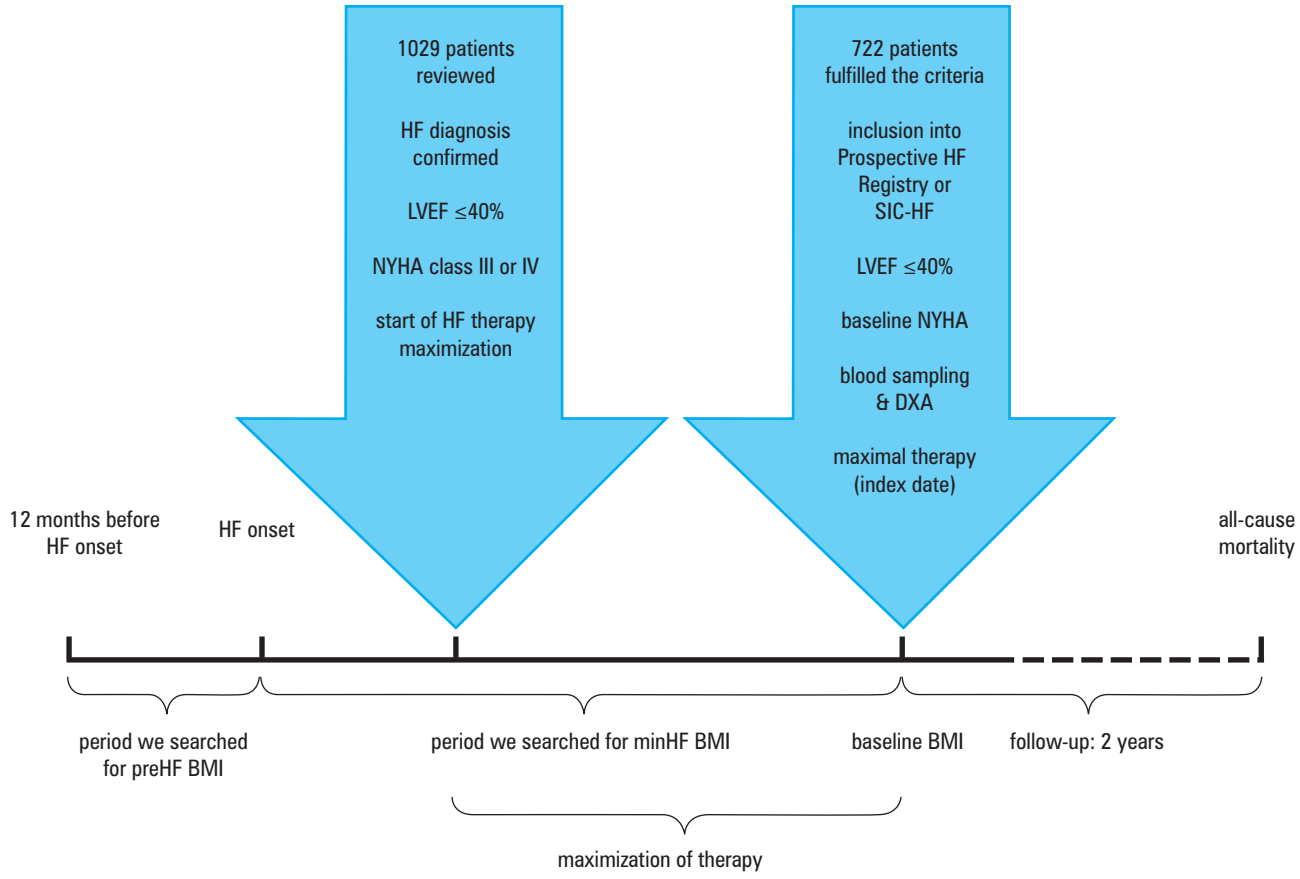

FIGURE 1 Flow chart of study procedures Abbreviations: BMI, body mass index; DXA, dual-energy X-ray absorptiometry; HF, heart failure; LVEF, left ventricular ejection fraction; minHF, minimum BMI after the onset of HF; NYHA, New York Heart Association; preHF, maximum BMI before the onset of HF;

weight gain (%) = 100 × (baseline BMI – minHF BMI) / minHF BMI

We used the Sonos-5000 Hewlett-Packard Ultrasound Scanner (Hewlett-Packard, Andover, Massachusetts, United States) to measure LVEF from the apical 4-chamber view and calculated it using the following formula:

LVEF = ([end-diastolic volume – end-systolic volume] / end-diastolic volume) × 100

Bone mineral density was measured using dual-energy X-ray absorptiometry with a pencil beam Lunar DRX-L device, (General Electric, Brussels, Belgium).

The serum levels of creatinine, albumin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), phosphorus, calcium, and the activity of alkaline phosphatase were measured using commercially available reagents (Roche Diagnostics, Switzerland). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula:

$eGFR_{MDRD} = 186 \times \text{serum creatinine (mg/dl)}^{-1.154} \times \text{age (years)}^{-0.203} \times 0.742$ (if female).

If serum albumin levels were lower than 40 g/l, we corrected calcium using the following formula:

corrected calcium (mmol/l) = total calcium + 0.02 × (40 – plasma albumin [g/l]).

A fasting urine sample collected in the morning was used to measure urinary creatinine, calcium, and phosphorus concentrations and allowed to calculate fractional urinary calcium and phosphorus excretion (FE_{Ca} and FE_{Pi}, respectively) using the following formula:

FE_{Ca} (or FE_{Pi}) = 100% × (urinary calcium [or phosphorus] × serum creatinine) / (serum calcium [or phosphorus] × urinary creatinine)

Based on the published data, the reference range for corrected serum calcium levels is from 2.10 to 2.54 mmol/l.[12] The values lower than 2.10 mmol/l and higher than 2.54 mmol/l were considered as hypocalcemia and hypercalcemia, respectively.

Statistical analysis Continuous variables were presented as mean values and standard deviation; categorical values, as percentages. For parameters with skewed distribution, median values and interquartile ranges were given. To ensure normal distribution for highly skewed variables (NT-proBNP, hs-CRP, $eGFR_{MDRD}$), $\log_{10}$ transformed values were used (in tables shown before transformation). Low, normal, and high serum calcium levels were defined based on the accepted criteria. The prevalence of calcium abnormalities in the subgroups defined by the NYHA class and quartiles of NT-proBNP was compared using the Cochrane–Armitage test. The comparison of clinical and laboratory parameters between various calcium levels was made by means of the Kruskal–Wallis or χ^2 test where appropriate with a post hoc analysis using the respective tests for multiple comparisons. A logistic regression analysis was used to assess the risk of calcium abnormalities in a subgroup of NYHA classes III–IV compared with that of NYHA classes I–II and a subgroup of NT-proBNP values higher than median compared with a subgroup with the levels

TABLE 1 Clinical and laboratory findings

Feature	All, n = 722	Hypocalcemia, n = 166	Normal calcium levels, n = 493	Hypercalcemia, n = 63	*P* value
demographic and clinical characteristics					
sex (women), %	13	11	12	22	0.07
age, y, mean ± SD	53 ±10	53 ±10	53 ±10	54 ±9	0.87
BMI at baseline, kg/m^2, mean ± SD	27 ±4	27 ±4	27 ±4	25 ±5	0.09
ischemic etiology of HF, %	67	74	64	67	0.07
duration of HF, mo, median (IQR)	48 (83)	36 (89)	33 (80)	41 (90)	0.58
systolic blood pressure, mmHg, mean ± SD	109 ±16	110 ±16	110 ±17	105 ±14	0.1
NYHA class before therapy maximization (III / IV), n	433 / 289	112 / 54[a]	296 / 197	24 / 39[c,e]	<0.001
NYHA class after therapy maximization, (I / II / III / IV), n	38 / 278 / 341 / 65	17 / 75 / 63 / 11[a]	21 / 186 / 244 / 41	0 / 17 / 34 / 13[c,d]	0.001
NYHA class change on treatment (W or N / Imp)	241 / 481	44 / 123[a]	173 / 320	24 / 38	<0.001
weight loss from preHF BMI to baseline BMI, %, median (IQR)	6.8 (13.7)	4.8 (12.5)[a]	6.7 (13.9)	12.8 (12.6)[b,f]	<0.001
weight gain from minHF to baseline BMI, %, median (IQR)	3.9 (10.1)	5.1 (8.5)	3.8 (11.0)	1.7 (6.7)	0.45
total bone mineral density, g/cm^2, mean ± SD	1.19 ±0.1	1.19 ±0.1	1.19 ±0.1	1.16 ±0.12	0.08
LVEF, %, mean ± SD	24 ±7	25 ±6	24 ±10	24 ±7	0.25
laboratory findings					
$eGFR_{MDRD}$, ml/min/1.73m^2, median (IQR)	86 (36)	86 (40)	86 (35)	82 (39)	0.49
albumin, g/l, mean ± SD	42 ±4	44 ±3[c]	42 ±4	38 ±5[c,f]	<0.001
alkaline phosphatase, IU, mean ± SD	82 ±46	73 ±29[a]	81 ±45	111 ±70[c,f]	<0.001
NTproBNP, pg/ml, median (IQR)	1497 (2752)	1083 (2019)[a]	1568 (2682)	3084 (4334)[c,f]	<0.001
hs-CRP, mg/l, median (IQR)	3.0 (5.6)	2.8 (5.2)	2.8 (5.0)	5.8 (14.5)[c,f]	0.009
phosphorus, mmol/l, mean ± SD	1.1 ±0.2	1.05 ±0.21[c]	1.13 ±0.23	1.23 ±0.27[b,f]	<0.001
corrected calcium, mmol/l, mean ± SD	2.30 ±0.20	2.02 ±0.1[c]	2.31 ±0.1	2.67 ±0.1[c,f]	<0.001
FE_{Ca}, n (mean ± SD)	269 (0.03 ±0.03)	45 (0.01 ±0.01)	209 (0.03 ±0.03)	15 (0.04 ±0.02)	0.2
FE_{Pi}, n (mean ± SD)	269 (16.8 ±9.8)	45 (16.7 ±8.7)	209 (16.9 ±10.0)	15 (15.6 ±7.3)	0.9
comorbidities, n (%)					
hypertension	403 (56)	101 (61)	268 (54)	34 (54)	0.4
type 2 diabetes	217 (30)	46 (28)	145 (29)	26 (41)	0.1
hypercholesterolemia	433 (60)	96 (58)	302 (61)	35 (56)	0.5
history of smoking	498 (69)	88 (53)[c]	366 (74)	44 (70)	<0.001
pharmacotherapy, percentage of treated patients (mean percentage of the recommended dose ± SD)					
ACEI / ARB	93 (58 ±52)	94 (56 ±43)	93 (59 ±54)	81 (49 ±62)	0.6
β-blockers	98 (45 ±28)	98 (42 ±25)	98 (47 ±28)	95 (45 ±30)	0.7
aldosterone antagonists	92 (123 ±67)	90 (120 ±74)	92 (123 ±65)	92 (127 ±64)	0.7
loop diuretics	88	84	88	90	0.3
thiazides	8	4[c]	10	10[e]	0.05
digoxin	48	42	49	57	0.1
all-cause mortality					
crude mortality rate at 2 years, %	24.1	20.5	24.5	30.2	0.3

post hoc *P* value: **a** <0.05, **b** <0.01, **c** <0.001 vs normal calcium levels
post hoc *P* value: **d** <0.05, **e** <0.01, **f** <0.001 vs hypocalcemia

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; $eGFR_{MDRD}$, estimated glomerular filtration rate using the Modification of Diet in Renal Disease formula; FE_{Ca}, fractional urinary calcium excretion; FE_{Pi}, fractional urinary phosphorus excretion; hs-CRP, high-sensitivity C-reactive protein; Imp, functional improvement of NYHA class after maximization of pharmacotherapy; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; W or N, worsening or no change of NYHA class after maximization of therapy, see **FIGURE 1**

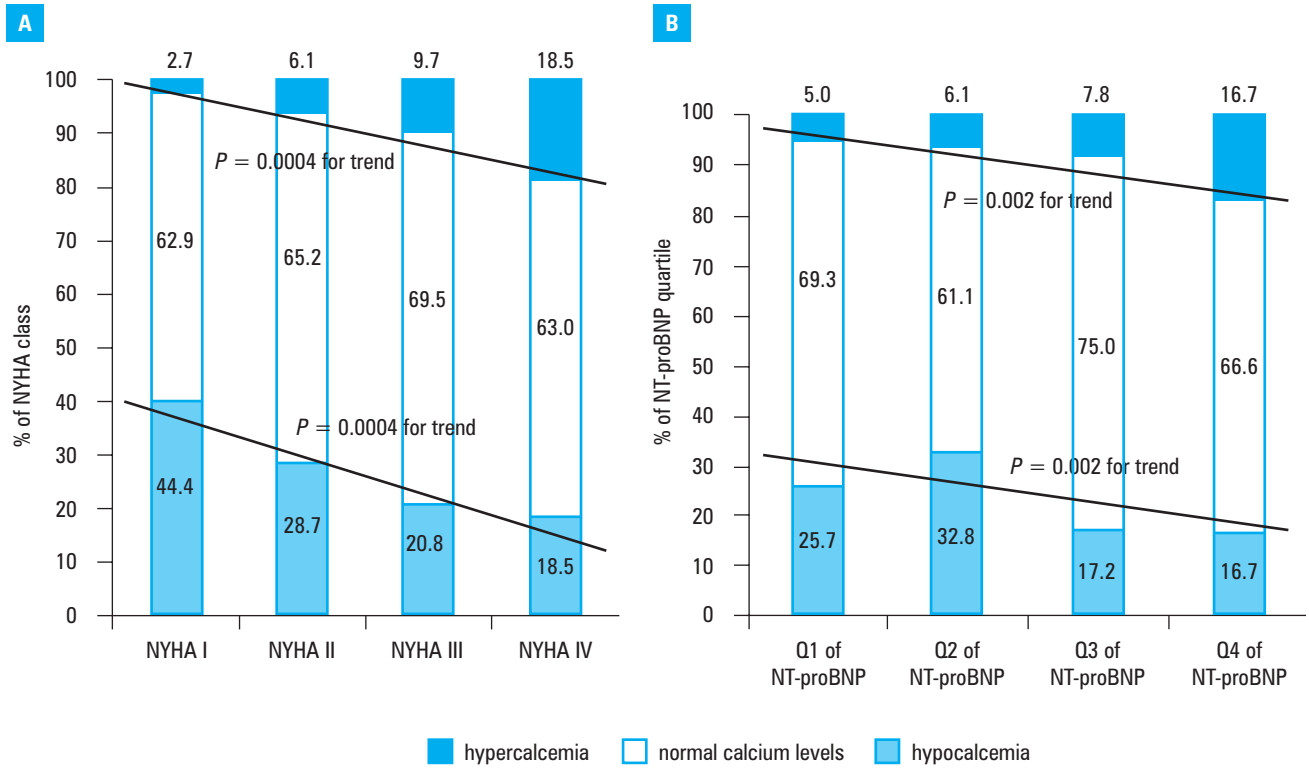

FIGURE 2 Distribution of calcium abnormalities after therapy maximization according to New York Heart Association (NYHA) functional class (**A**) and quartiles of N-terminal pro-B-type natriuretic peptide (NT-proBNP) (**B**)

lower than the median. A logistic regression was also used to identify univariate and multivariate predictors of abnormal calcium levels in relation to normal ones. Parameters with a *P* value of less than 0.05 in a univariate analysis were included in the multivariate models. Owing to a limited number of cases in the hypercalcemia group, only 6 most significant univariate predictors were entered into the multivariate hypercalcemia risk model. The stepwise forward selection was used and a *P* value for inclusion into the multivariate model was set at a level of 0.05 and lower. Then, we constructed Kaplan–Meier cumulative survival curves and used the log-rank test for comparison. Finally, the Cox proportional hazard analysis was used to estimate the adjusted risk of death in the groups with abnormal calcium levels in relation to the group with normal calcium levels. Data on mortality were obtained from the national identification number database (PESEL, *Powszechny Elektroniczny System Ewidencji Ludności*). A significance level was set at 0.05 (2-tailed), and all calculations were performed using the software packages of Statistica v. 10.0 and NCSS v2007.

RESULTS

New York Heart Association class during therapy maximization

Overall, during HF therapy escalation, the NYHA class improved at least by 1 in 481 patients (66.6%). Of the remaining 241 patients (33.4%), the NYHA class did not change in 224 patients (31.0%) and worsened in 17 (2.4%). Of the 433 patients with NYHA class III at baseline, an improvement was noticed in 240 (55.3%). In 289 patients with NYHA class IV at baseline, the class improved in 241 patients (83.3%) after therapy maximization. Patients diagnosed as hypocalcemic after therapy maximization were classified mainly as NYHA class III at baseline, while those diagnosed as hypercalcemic, as NYHA class IV. In the hypocalcemic group, 74.1% of the patients responded favorably to therapy compared with 64.6% and 60.3% of the patients with normal calcium levels and with hypercalcemia, respectively. The overall clinical characteristics of all patients and of subgroups with different serum calcium levels are shown in TABLE 1.

Prevalence of abnormal serum calcium levels following maximization of therapy

Abnormal serum calcium levels were present in 229 patients (31.7%). Hypocalcemia was the most prevalent abnormality; it was reported in 166 patients (23.0%). In the remaining 63 patients (8.7%), hypercalcemia was observed. Normal calcium levels were noted in 8.7% of the patients.

Distribution and risk of abnormal serum calcium levels according to the severity of heart failure following maximization of therapy

Abnormalities in serum calcium levels varied depending on the NYHA class. The prevalence of hypercalcemia increased significantly with an increasing NYHA class (P = 0.0004 for trend). Hypocalcemia was most common in patients with NYHA class I, and its prevalence decreased with a more advanced NYHA class (P = 0.0004 for trend; FIGURE 2A). The subgroup analysis of NT-proBNP quartiles showed a similar distribution pattern (P = 0.002 for trend both for hypocalcemia and hypercalcemia; FIGURE 2B).

The risk analysis of hypocalcemia, both unadjusted and after an adjustment for age, sex, BMI, etiology of HF, $eGFR_{MDRD}$, and the use of thiazides, showed a lower risk of hypocalcemia (by approximately 20%) in these patients who despite therapy optimization still remained in NYHA class III or IV as compared with those who improved

TABLE 2 Odds ratios for dyscalcemia and response to heart failure therapy

Feature	Hypocalcemia		Hypercalcemia	
	OR, 95% CI	*P* value	OR, 95% CI	*P* value
improved to NYHA I or II (reference)	1.0		1.0	
remaining in NYHA III or IV (unadjusted analysis)	0.78, 0.65–0.93	0.006	1.34, 1.01–1.80	0.04
remaining in NYHA III+IV (adjusted for age, sex, BMI, etiology of HF, $eGFR_{MDRD}$, use of thiazides)	0.79, 0.64–0.98	0.03	1.43, 1.01–2.030.04	0.04
bellow median of NT-proBNP (reference)	1.0		1.0	
above or equal to median of NT-proBNP (unadjusted analysis)	0.73, 0.61–0.88	0.001	1.40, 1.06–1.86	0.02
above of equal to median NT-proBNP (adjusted for age, sex, BMI, etiology of HF, $eGFR_{MDRD}$, use of thiazides)	0.77, 0.62–0.96	0.02	1.43, 1.02–2.0	0.03

Abbreviations: CI, confidence interval; OR, odds ratio; others, see FIGURE 1 and TABLE 2

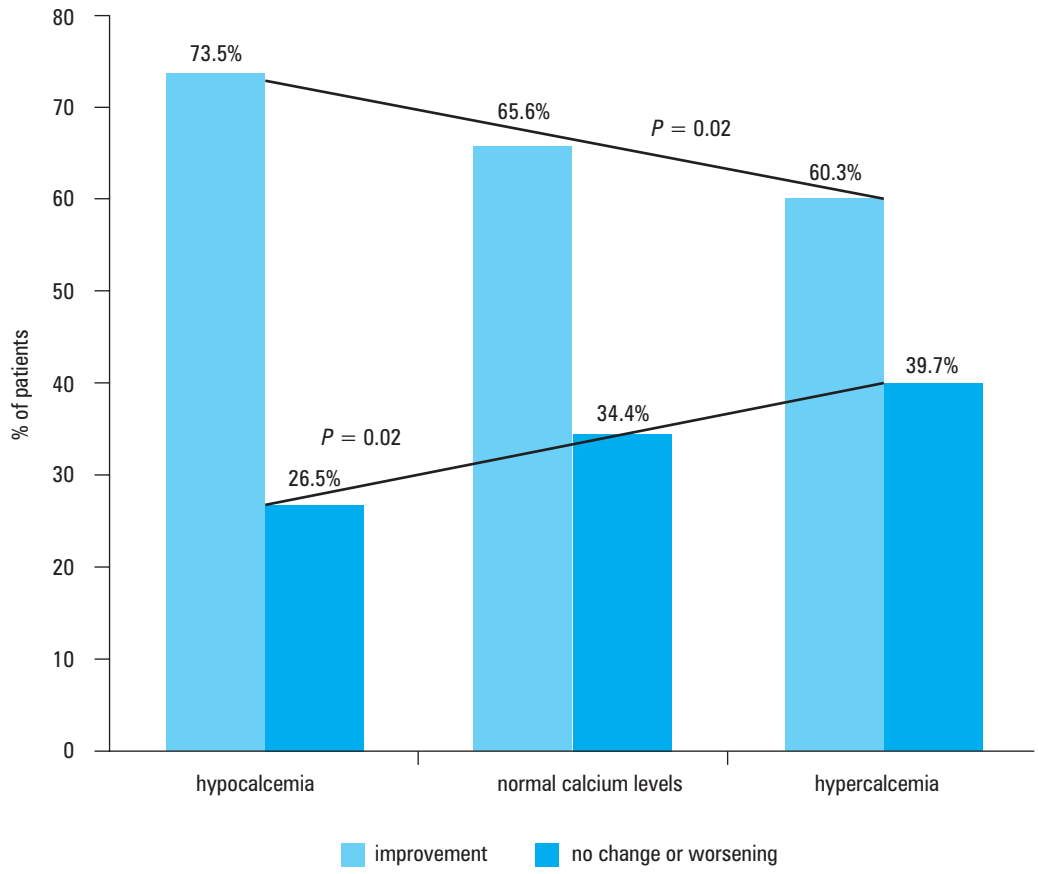

FIGURE 3 Clinical response to therapy maximization in subgroups with different serum calcium levels

to NYHA class I or II ($P = 0.006$ and $P = 0.03$, respectively; TABLE 2). In the analysis of NT-proBNP, both unadjusted and adjusted models revealed a lower risk of hypocalcemia in the subgroup with NT-proBNP levels equal or above the median compared with the subgroup with the levels below the median ($P = 0.001$ and $P = 0.02$, respectively; TABLE 2). In either the NYHA or NT-proBNP subgroup analysis, the significance of the adjusted models was lost after the further adjustment for a change in the NYHA class following therapy maximization ($P = 0.09$ for both, data not shown). The risk analysis of hypercalcemia, both for a higher NYHA class and NT-proBNP, provided similar findings to those for hypocalcemia (TABLE 2). The adjustment for a change in the NYHA class following therapy maximization did not affect the risk level (data not shown).

Calcium abnormalities and response to therapy The improvement of the NYHA class was most common in patients who were hypocalcemic after HF therapy was optimized, while a favorable response to therapy was less frequent in those who were later diagnosed as hypercalcemic. There was a significant difference in the change in the functional status following treatment between patients with different serum calcium levels ($P = 0.02$; FIGURE 3).

Predictors of abnormal serum calcium levels: univariate and multivariate analysis The clinical and laboratory profiles of patients with abnormal serum calcium levels differed from those of patients with normal levels. Clinical and laboratory characteristics of the study groups and comparisons between the groups are shown in TABLE 1.

TABLE 3 Univariate and multivariate predictors of hypercalcemia vs normal serum calcium

Feature	Hypercalcemia (OR, 95% CI)			
	univariate	*P* value	multivariate	*P* value
sex (female vs male)	1.44, 1.03–2.00	0.03		
baseline BMI (per 1 kg/m^2 increase)	0.94, 0.88–0.99	0.05		
systolic blood pressure (per 5 mmHg increase)	0.91, 0.82–0.99	0.04		
NYHA class (per 1 class increase)	1.73, 1.17–2.56	0.005		
weight loss (per 5% increase)	1.25, 1.10–1.42	<0.001		
total bone mineral density (per 0.1 g/cm^2 decrease)	0.73, 0.55–0.97	0.03		
albumin (per 1 g/l decrease)	1.31, 1.22–1.42	<0.001	1.38, 1.23–1.55	<0.001
alkaline phosphatase (per 10 IU increase)	1.03, 1.06–1.13	0.03		
NT-proBNP (per 1000 pg/ml increase)	1.10, 1.02–1.18	0.008		
hs-CRP (per 1 mg/l increase)	1.02, 1.01–1.03	<0.001		
phosphorus (per 0.2 mmol/l increase)	1.34, 1.10–1.64	0.003	1.53, 1.59–1.56	0.009
type 2 diabetes mellitus (yes vs no)	1.29, 0.98–1.69	0.06		
ACEI/ARB[a]	0.76, 0.57–1.02	0.07		
Feature	**Hypocalcemia (OR, 95% CI)**			
	univariate	*P* value	multivariate	*P* value
etiology (ischemic vs nonischemic)	1.26, 1.03–1.53	0.02		
NYHA class (per 1 class increase)	0.69, 0.54–0.89	0.004		
NYHA class change on treatment (W or N / Imp)	0.82, 0.67–0.99	0.04		
weight loss, (per 5% increase)	0.93, 0.86–1.00	0.05		
albumin (per 1 g/l increase)	1.15, 1.09–1.21	<0.001	1.15, 1.08–1.22	<0.001
alkaline phosphatase (per 10 IU increase)	0.94, 0.89–0.99	0.03		
phosphorus (per 0.2 mmol/l decrease)	1.42, 1.19–1.70	<0.001	1.43, 1.18–1.74	<0.001
history of smoking (yes vs no)	0.62, 0.51–0.74	<0.001	0.41, 0.21–0.63	<0.001
aldosterone antagonists[a]	0.82, 0.65–1.03	0.08		
thiazides (yes vs no)	0.59, 0.38–0.92	0.02	0.46, 0.19–0.98	0.02

a the risk in patients receiving more than median vs less than median percent of a target recommended dose

Abbreviations: see FIGURE 1 and TABLES 1 and 2

In the univariate analysis, several parameters predicted hypercalcemia but only 2 remained significant in the multivariate model comprising 6 variables most significant in the univariate analysis (NYHA class, weight loss, albumin, NT-proBNP, hs-CRP, and phosphorus). A decrease in the albumin concentration by 1 g/l was associated with an increase in the risk of hypercalcemia by 38%, whereas an increase in serum phosphorus levels by 0.2 mmol/l was associated with an increase in the risk of hypercalcemia by 53%. The final multivariate model explained 26.9% of variance in hypercalcemia (TABLE 3).

Hypocalcemia had 10 significant univariate predictors. In the multivariate model comprising all 10 parameters, only 4 remained significant. An increase in the albumin concentration by 1 g/l and a decrease in serum phosphorus levels by 0.2 mmol/l were associated with an increase in the risk of hypocalcemia by 15% and 43%, respectively. Finally, a history of smoking and treatment with thiazides reduced the risk of hypocalcemia by 59% and 54%, respectively. The final multivariate model explained only 11.1% of the total variance in hypocalcemia (TABLE 3).

Abnormal serum calcium levels and 2-year mortality At 2 years, 174 patients (24.1%) died, of whom 34 (20.5%) belonged to the hypocalcemia group; 19 (30.2%), to the hyperglycemia group; and 121 (24.5%) had normal calcium levels. The cumulative survival curves showed no difference in mortality between the respective groups (P = 0.26; FIGURE 4).

Compared with the group with normal serum calcium levels, the unadjusted hazard ratio (HR) of all-cause mortality at 2 years in patients with hypocalcemia was 0.79 (95% confidence interval [CI], 0.54–1.17; P = 0.24). In this group, the model adjusted for age, sex, and the change in NYHA class during treatment showed a HR of 0.86 (95% CI, 0.58–1.25; P = 0.43), and the only significant predictor of death in this multivariate model was the change in NYHA class (P <0.001).

A similar unadjusted analysis for hypercalcemic patients showed a HR of 1.23 (95% CI, 0.76–2.00; P = 0.38). The adjustment for age, sex, and change in NYHA class did not significantly affect the risk (HR, 1.21; 95% CI, 0.74–1.98; P = 0.44), and the change in NYHA class was not significant in this model.

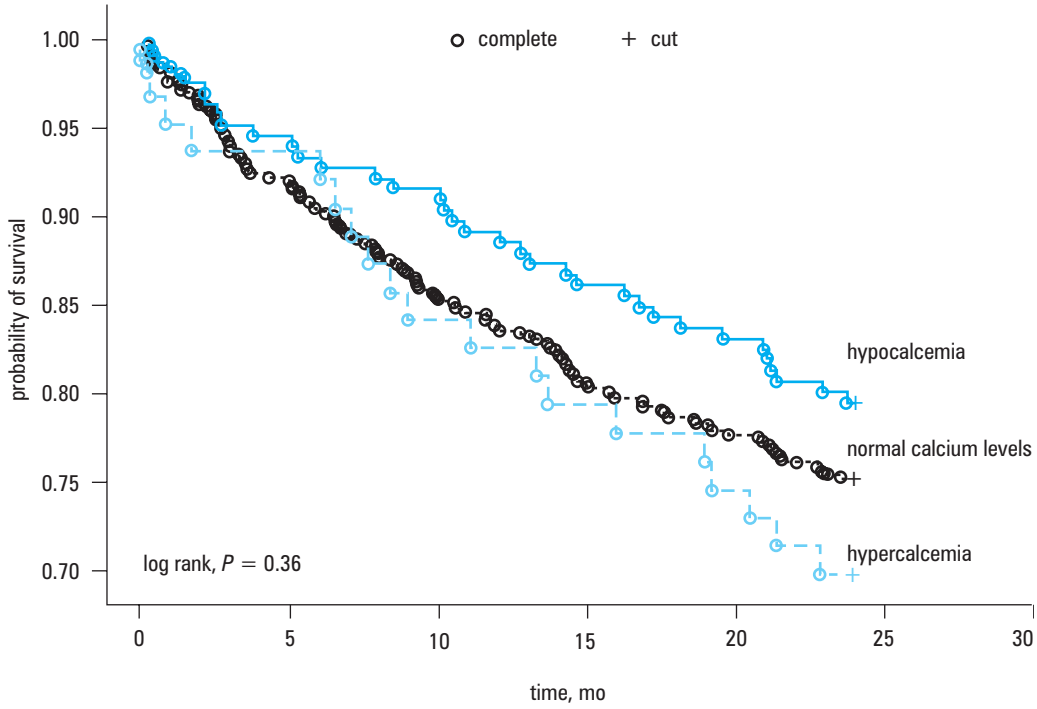

FIGURE 4 Cumulative survival curves in groups of serum calcium during a 2-year follow-up

DISCUSSION Dysregulation of calcium homeostatic mechanisms is common in HF.[13] There have been numerous studies in patients treated at intensive care units (including those with acute HF) that showed a high prevalence of hypocalcemia and its association with poor prognosis.[14] Importantly, correction of hypocalcemia with intravenous calcium in certain clinical settings was associated with higher mortality.[7] In contrast to acute HF, epidemiological data on abnormal serum calcium levels in patients with stable HF receiving optimal treatment are scarce. Most of the available studies were small,[15,16] pharmacotherapy affecting serum calcium was not reported,[16] or important confounders such as kidney function were not taken into account.[15]

Both hypocalcemia and hypercalcemia may adversely affect cardiovascular function. Calcifications of various cardiovascular structures were shown in hypercalcemia, while induction or aggravation of existing HF was repeatedly demonstrated in hypocalcemia.[17] The pathophysiological effects of calcium treatment of hypocalcemia occurring in the course of acute conditions are in sharp contrast with a response noticed after calcium and vitamin D supplementation given to patients with hypocalcemia complicated by HF.[18,19] This difference highlights the complexity of calcium metabolism and our poor understanding of the role of hypocalcemia in the pathophysiology of various HF syndromes.

In everyday life, most patients stabilized after acute HF (both de novo or chronic HF decompensation) usually had their therapy started and doses titrated without measuring their baseline serum calcium levels. The diagnosis of hypocalcemia in patients who improved their functional status after therapy maximization may be perplexing to clinicians because hypocalcemia is usually associated with worsened HF. Additionally, the diagnosis of hypocalcemia when the optimal therapy has been reached may justify calcium and/or vitamin D supplementation, while safety and potential benefits of such an intervention remain unclear. Therefore, we believe that our findings are novel and have clinical relevance. We emphasize the importance of serum calcium measurement during the initial medical checkup of a patient with HF.

Our study was not designed to investigate the pathophysiology of calcium abnormalities. Rather, we intended to attract the attention of practicing physicians to a phenomenon that had not been previously reported. Below we discuss a potential mechanism that should be investigated in dedicated studies.

Typical HF treatment may exert significant effects on bone metabolism with a potential change in serum calcium levels. For example, in an experimental fracture in a mouse model, the use of perindopril accelerated femur bone healing.[20] Moreover, in ovariectomized rats, captopril improved osteopenia and promoted bone formation.[21] In both models, calcium availability was needed for bone accrual.

Propranolol given to ovariectomized rats with osteoporosis improved bone porosity and decreased serum alkaline phosphatase activity similarly to the effect of zoledronic acid and alphacalcidol.[22] A surgical treatment of primary hyperparathyroid patients resulting in a decrease in parathormone (PTH) levels to those commonly observed in HF, led to a parallel decrease in PTH and serum calcium levels, while bone mineral density increased.[13,23] A similar PTH-lowering effect was observed after the administration of aldosterone blockers.[24]

Based on the above findings, it is tempting to speculate that in HF patients with a diet possibly low in calcium or impaired gut absorption due to

vitamin D deficiency, the inhibition of PTH secretion by aldosterone antagonists may induce an effect mimicking hungry bone syndrome resulting in hypocalcemia. This syndrome occurs in hyperparathyroid patients after surgery when a rapid withdrawal of PTH action on the bone induces a prompt apposition of calcium into the unmineralized bone matrix.[25] In HF, a mismatch between a diet low in calcium or impaired gut absorption and the metabolic needs of the bone may be further aggravated by anabolic effects of ACEIs, ARBs, and β-blockers.

There are several arguments to support our hypothesis. In the multivariate analysis, we showed a negative correlation of the smoking history and use of thiazides with hypocalcemia. This may be explained by the fact that smoking impairs osteoblast function, thereby decreasing the ability of the bones to absorb calcium and phosphorus from the blood.[26] Furthermore, thiazides inhibit urinary calcium wasting, thereby increasing serum calcium levels.[27] Therefore, both of the above mechanisms may oppose the development of hypocalcemia. Our hypothesis is also supported by an observation that higher albumin and lower phosphorus levels were significant predictors of hypocalcemia in the multivariate analysis. Higher albumin levels may reflect a better nutritional status likely resulting from a catabolic-to-anabolic switch. The same mechanism may be responsible for low serum phosphorus levels because hypophosphatemia usually occurs as a consequence of accelerated anabolism during refeeding.[28] The dose of aldosterone antagonists was unusually high in our study. By preventing urinary calcium loss and reducing hypocalcemia, aldosterone antagonists may indirectly inhibit PTH and cause functional hypoparathyroidism in susceptible patients. Of note, patients with hypocalcemia had the mean fractional calcium excretion into urine 3 times lower than patients with normal serum calcium levels. This observation excludes the possibility of urinary calcium loss as the cause of hypocalcemia. Although FE_{ca} in hypocalcemia was not significantly different from that in the other groups, lower FE_{ca} in hypocalcemia might be interpreted as renal adaptation to low serum calcium levels induced by nonrenal causes. Taken together, the occurrence of hypocalcemia in patients with a therapy-induced improvement of NYHA class, simultaneous improvement of nutritional markers, and at least as good a prognosis as in patients with normal calcium levels, might be interpreted as the result of a mild form of the hungry bone effect. Importantly, almost 90% of variance in hypocalcemia cannot be explained by predictors included in our analysis. It highlights the role of other factors that were not analyzed in this study (possibly diet, vitamin D, and PTH pathways). Additional studies are needed to clarify the role of calcium supplementation alone or in combination with vitamin D in hypocalcemic patients.

It is difficult to suggest a pathophysiological explanation for hypercalcemia. The lack of increased phosphaturia, as measured by the fractional urinary excretion of phosphorus in hypercalcemic patients, casts doubt on hyperparathyroidism as the cause of hypercalcemia. Conversely to hypocalcemia, hypercalcemia might have resulted from the lack of a switch from a catabolic to more anabolic profile. This notion is supported by observations of a worse nutritional status as represented by lower albumin levels, higher neuroactivation shown by NT-proBNP, and more extensive inflammation. The latter has recently emerged as an important pathophysiological contributor to bone disintegration and lower bone mineral density, which was also observed in our patients with hypercalcemia.[29]

Strengths and limitations Our study is the first to have shown serum calcium profiles in HF patients from everyday practice and with varying clinical response to modern intensive therapy. Contrary to common belief, the study documents the presence of hypocalcemia mostly in patients positively responding to treatment and questions the association between hypocalcemia related to HF treatment maximization and worse clinical outcome. We are the first to hypothesize that the switch from the anabolic to catabolic profile is a potential mechanism responsible for these findings.

Our study has several limitations. The retrospective design made it impossible to draw any conclusions on causality. The lack of knowledge on serum calcium levels at baseline might have resulted in a significant bias. Rather than ionized calcium, we measured total serum calcium levels, which even after adjustment for albumin might have not exactly reflected true calcium levels. The threshold values defining particular mineral abnormalities are not uniformly accepted. Although the change of those thresholds might have significantly modified the prevalence of a given abnormality, it could not have modified the relation of calcium abnormalities to HF severity. Finally PTH measurements were not available, and we could not confirm the expected decrease in PTH levels following treatment.

Conclusions Serum calcium abnormalities are linked to a response to HF therapy and to HF severity after therapy maximization. Hypocalcemia that develops following maximization of HF therapy is associated with a clinical improvement and does not carry excessive risk. Hypercalcemia occurs more frequently in patients who do not respond to therapy and is associated with a more catabolic laboratory profile. However, further studies are needed to establish its clinical significance.

Contribution statement PR conceived the idea of the study. PR, JN, and LP contributed to the design of the research. All authors were involved in data collection. PR, JN, and BH analyzed the data. All authors edited and approved the final version of the manuscript.

Acknowledgments The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement No. 241558 (SICA-HF), granted to SDA.

REFERENCES

1 Breitwieser GE. Extracellular calcium as an integrator of tissue function. Int J Biochem Cell Biol. 2008; 40: 1467-1480.

2 Magno AL, Ward BK, Ratajczak T. The calcium-sensing receptor: a molecular perspective. Endocr Rev. 2011; 32: 3-30.

3 Rywik TM, Koziarek J, Piotrowski W, et al. Trends in heart failure mortality in Poland between 1980 and 2010. Pol Arch Med Wewn. 2013; 123: 664-671.

4 von Haehling S, Lainscak M, Springer J, Anker SD. Cardiac cachexia: a systematic overview. Pharmacol Ther. 2009; 121: 227-252.

5 Borkowski BJ, Cheema Y, Shahbaz AU, et al. Cation dyshomeostasis and cardiomyocyte necrosis: the Fleckenstein hypothesis revisited. Eur Heart J. 2011; 32: 1846-1853.

6 Steele T, Kolamunnage-Dona R, Downey C, et al. Assessment and clinical course of hypocalcemia in critical illness. Critical Care. 2013; 17: R106.

7 Collage RD, Howell GM, Zhang X, et al. Calcium supplementation during sepsis exacerbates organ failure and mortality via calcium/calmodulin-dependent protein kinase kinase signaling. Crit Care Med. 2013; 41: e352-e360.

8 McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012; 33: 1787-1847.

9 Chavan CB, Sharada K, Rao HB, Narsimhan C. Hypocalcemia as a cause of reversible cardiomyopathy with ventricular tachycardia. Ann Intern Med. 2007; 146: 541-542.

10 Lundgren E, Lind L, Palmer M, et al. Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years. Surgery. 2001; 130: 978-985.

11 von Haehling S, Lainscak M, Doehner W, et al. Diabetes mellitus, cachexia and obesity in heart failure: rationale and design of the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF). J Cachexia Sarcopenia Muscle. 2010; 1: 187-194.

12 Eckardt K-U, Kasiske BL. KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int. 2009; 76: S1-S130.

13 Shane E, Mancini D, Aaronson K, et al. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. Am J Med. 1997; 103: 197-207.

14 Steele T, Kolamunnage-Dona R, Downey C, et al. Assessment and clinical course of hypocalcemia in critical illness. Crit Care. 2013; 17: R106.

15 Arakelyan KP, Sahakyan YA, Hayrapetyan LR, et al. Calcium-regulating peptide hormones and blood electrolytic balance in chronic heart failure. Regul Pept. 2007; 142: 95-100.

16 Garakyaraghi M, Kerdegari M, Siavash M. Calcium and vitamin D status in heart failure patients in Isfahan, Iran. Biol Trace Elem Res. 2010; 135: 67-73.

17 Maiya S, Sullivan I, Allgrove J, et al. Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. Heart. 2008; 94: 581-584.

18 Kazmi AS, Wall BM. Reversible congestive heart failure related to profound hypocalcemia secondary to hypoparathyroidism. Am J Med Sci. 2007; 333: 226-229.

19 Bansal B, Bansal M, Bajpai P, Garewal HK. Hypocalcemic cardiomyopathy-different mechanisms in adult and pediatric cases. J Clin Endocrinol Metab. 2014; 99: 2627-2632.

20 Garcia P, Schwenzer S, Slotta JE, et al. Inhibition of angiotensin-converting enzyme stimulates fracture healing and periosteal callus formation - role of a local renin-angiotensin system. Br J Pharmacol. 2010; 159: 1672-1680.

21 Liu YY, Yao WM, Wu T, et al. Captopril improves osteopenia in ovariectomized rats and promotes bone formation in osteoblasts. J Bone Miner Metab. 2011; 29: 149-158.

22 Khajuria DK, Razdan R, Mahapatra DR, Bhat MR. Osteoprotective effect of propranolol in ovariectomized rats: a comparison with zoledronic acid and alfacalcidol. J Orthop Sci. 2013; 18: 832-842.

23 Dy BM, Grant CS, Wermers RA, et al. Changes in bone mineral density after surgical intervention for primary hyperparathyroidism. Surgery. 2012; 152: 1051-1058.

24 Salcuni AS, Palmieri S, Carnevale V, et al. Bone involvement in aldosteronism. J Bone Miner Res. 2012; 27: 2217-2222.

25 Karsenty G, Ferron M. The contribution of bone to whole-organism physiology. Nature. 2012; 481: 314-320.

26 Yoon V, Maalouf NM, Sakhaee K. The effects of smoking on bone metabolism. Osteoporos Int. 2012; 23: 2081-2092.

27 Nijenhuis T, Hoenderop JG, Loffing J, et al. Thiazide-induced hypocalciuria is accompanied by a decreased expression of Ca2+ transport proteins in kidney. Kidney Int. 2003; 64: 555-564.

28 Skipper A. Refeeding syndrome or refeeding hypophosphatemia: a systematic review of cases. Nutr Clin Pract. 2012; 27: 34-40.

29 Walsh NC, Gravallese EM. Bone remodeling in rheumatic disease: a question of balance. Immunol Rev. 2010; 233: 301-312.

ARTYKUŁ ORYGINALNY

Nieprawidłowe stężenie wapnia w surowicy a eskalacja terapii niewydolności serca

Piotr Rozentryt[1], Jacek T. Niedziela[1], Bartosz Hudzik[1], Wolfram Doehner[2], Ewa A. Jankowska[3], Jolanta Nowak[1], Stephan von Haehling[4], Krzysztof Myrda[1], Stefan D. Anker[4], Piotr Ponikowski[3], Lech Poloński[1]

1 III Katedra i Oddział Kliniczny Kardiologii, Śląskie Centrum Chorób Serca, Śląski Uniwersytet Medyczny, Zabrze
2 Centre for Stroke Research Berlin, Charité Medical School, Berlin, Niemcy
3 Ośrodek Chorób Serca, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu, Wrocław
4 Applied Cachexia Research, Department of Cardiology, Charité Medical School, Campus Virchow-Klinikum, Berlin, Niemcy

SŁOWA KLUCZOWE

epidemiologia, nieprawidłowe stężenie wapnia, odpowiedź na terapię, śmiertelność, zaawansowanie objawów niewydolności serca

STRESZCZENIE

WPROWADZENIE Nieprawidłowe stężenie wapnia w surowicy pogarsza czynność układu krążenia. Leczenie niewydolności serca (NS) może wpływać na utratę wapnia z moczem i jego odkładanie w kościach, a w konsekwencji – na kalcemię.

CELE Celem badania była ocena częstości nieprawidłowych stężeń wapnia we krwi u chorych podczas eskalacji terapii NS, określenie klinicznych i laboratoryjnych predyktorów nieprawidłowych stężeń wapnia w surowicy oraz zbadanie ich związku z rokowaniem.

PACJENCI I METODY Do badania włączono 722 chorych z NS wyjściowo w klasie NYHA III-IV (wiek 53 ±10 lat, 13% kobiet), u których terapia NS była modyfikowana do maksymalnych tolerowanych dawek.

WYNIKI W następstwie maksymalizacji terapii NS u 66,7% chorych klasa NYHA uległa poprawie co najmniej o jedną klasę, u 31,0% klasa NYHA nie zmieniła się, a u 2,4% uległa pogorszeniu. Hipokalcemia wystąpiła u 166 chorych (22.9%) i obserwowano ją częściej u osób z poprawą klasy NYHA. Hiperkalcemię rozpoznano u 63 pacjentów (8,7%), częściej u osób bez poprawy czynnościowej lub z pogorszeniem klasy NYHA. Efekt ten nie zależał od wieku, płci, etiologii NS, indeksu masy ciała, czynności nerek czy stosowania tiazydów. Hiperkalcemia wiązała się z większym nasileniem katabolizmu, gorszym profilem hemodynamicznym, bardziej nasilonym zapaleniem i niższą gęstością mineralną kości. Niższe stężenie albumin i wyższe fosforanów, niezależnie od czynności nerek, były predyktorami hiperkalcemii. Hipokalcemia wiązała się z mniej nasilonym katabolizmem, wyższym stężeniem albumin a niższym fosforanów, stosowaniem tiazydów i paleniem tytoniu. Zarówno hipokalcemia jak i hiperkalcemia nie wiązała się z gorszym rokowaniem.

WNIOSKI Nasze dane sugerują, że występowanie nieprawidłowych stężeń wapnia w surowicy u chorych z NS skojarzone jest z kliniczną odpowiedzią na maksymalizację farmakoterapii. Łagodna hipokalcemia występująca po optymalizacji leczenia nie pogarsza rokowania. Hiperkalcemia skojarzona jest z brakiem pozytywnej odpowiedzi na terapię, a jej znaczenie rokownicze pozostaje nieustalone.

Adres do korespondencji:
dr n. med. Piotr Rozentryt, III Katedra i Oddział Kliniczny Kardiologii, Śląskie Centrum Chorób Serca, Śląski Uniwersytet Medyczny, ul. M. Curie-Skłodowskiej 9, 41-800 Zabrze, tel.: 32-278-15-92, fax: 32-273-26-79, e-mail: p.rozentryt@sccs.pl
Praca wpłynęła: 11.11.2014.
Przyjęta do druku: 02.01.2015
Publikacja *online*: 12.01.2015.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2015; 125 (1-2): 54-64