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The value of cancer antigen 125 (Ca 125) and copeptin as markers in patients with advanced heart failure

Wartość oznaczania stężeń antygenu nowotworowego Ca 125 i kopeptyny w monitorowaniu terapii chorych z zaawansowaną niewydolnością serca

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Abstract

Introduction. A search continues for new markers and new monitoring methods that would be useful in the management of patients with advanced heart failure (HF). Recent studies have shown increased levels of cancer antigen 125 (Ca 125) and copeptin in patients with HF which implies that they may be used as markers of HF.

Material and methods. The aim of the study was to evaluate levels of potential HF markers in relation to established biochemical markers. The study included 60 patients who were admitted due to exacerbation of chronic New York Heart Association class III or IV systolic HF. Before administration of initial intravenous diuretic dose, blood samples were collected to determine levels of conventional prognostic factors (uric acid, B-type natriuretic peptide [BNP]) and novel HF biomarkers (Ca 125, copeptin).

Results. On admission, BNP level (median 1166.50 pg/mL [636.00–2068.50]) and uric acid level (9.497 ± 2.426 mg/dL) in patients with HF was significantly higher compared to respective normal values. Ca 125 level (median 88.71 U/mL [29.28–169.00]) was also significantly increased, and copeptin level was significantly higher compared to the control group (median 96.55 vs 7.05 pg/mL, $p < 0.0001$). In additional, a statistically significant correlation between baseline BNP and Ca 125 levels ($r = 0.48$, $p < 0.001$) was observed. No correlations were found between baseline levels of copeptin and BNP or uric acid.

Conclusion. In patients with chronic HF, several pathomechanisms are operating, which may be indicated by increased levels of several markers, including both conventional and new ones. Higher levels of Ca 125 were observed in patients with acute decompensated HF, even though these patients did not have a malignancy. However, Ca 125 did not exceed the prognostic value of BNP due to its low specificity. Despite different pathomechanisms of BNP and Ca 125 level elevations, a correlation was found between these markers, which might indicate a complex pathophysiology of HF in the studied group.

Key words: heart failure, biomarkers, Ca 125, copeptin, BNP

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Introduction

Heart failure (HF) is a major clinical and social problem. Despite improved treatment, HF is the only cardiovascular condition with an increasing prevalence, and the most common and costly reason for hospital admission among patients above 65 years of age. It has been estimated that costs of HF treatment amount for 1 to 2% of national healthcare expenditure, and more than 60% of these costs are related to inpatient treatment [1]. Established markers of HF include B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proNBP), and their use in clinical practice is recommended in the European Society of Cardiology (ESC) and American College of Cardiology/ /American Heart Association (ACC/AHA) guidelines. Search continues for new substances that would allow more precise identification of HF patients and effective monitoring of the condition. Such potential markers of HF include cancer antigen 125 (Ca 125) and copeptin.

Cancer antigen 125 is a glycoprotein from the mucin family, coded by a gene on human chromosome 19 and produced by serosal endothelial cells in response to fluid accumulation and/or cytokine production. Ca 125 is an established marker used to detect and monitor ovarian cancer. It has been recently shown that Ca 125 level is elevated also in patients with HF and correlates with the disease severity evaluated both clinically and based on haemodynamical and echocardiographic markers [2].

Copeptin is a C-terminal fragment of provasopressin, released in equimolar amounts with vasopressin but characterized by a much longer serum half-life compared to vasopressin, and significant stability ex vivo [3]. Seminal studies have shown that copeptin may be a predictor of survival following an acute coronary syndrome, as the vasopressin system is activated following myocardial infarction [4], and thus copeptin has been considered a potential cardiac biomarker by the National Academy of Clinical Biochemistry expert panel.

The aim of the study was to evaluate Ca 125 and copeptin levels in relation to established HF marker levels (BNP and uric acid) in patients with advanced chronic HF (chronic New York Heart Association [NYHA] class II–IV systolic HF with the left ventricular ejection fraction of < 45% treated for at least 3 months) admitted for acute decompensated HF.

Material and methods

The study included 60 patients with advanced HF who were admitted to a cardiology unit due to HF exacerbation defined as new symptoms or signs (*e.g.*, orthopnoea, signs of pulmonary congestion, pleural effusion, ascites, peripheral oedema) that required acute hospitalization and administration of intravenous diuretics. Patients with concomitant malignancy, acute and chronic inflammatory conditions, and liver or kidney failure (serum transaminase levels increased threefold above the upper limit of normal values or glomerular filtration rate [GFR] < 30 mL/ /min/1.73 m^2, respectively) were excluded from the study. All patients received optimal therapy according to the ESC guidelines on the management of acute and chronic HF. Blood samples for study measurements were collected on the day of admission

Laboratory testing

Plasma BNP level was measured by enzyme immunohistochemistry (AxSYM BNP). Serum Ca 125 level was measured by electrochemiluminescence (Elecsys Ca 125 II, manufacturer reference levels < 35 U/mL). Serum copeptin level was measured by the immunoenzymatic method (ELISA) (E90365 Hu, USCN). As no established reference values are available for copeptin level, we used a control group that included 20 healthy volunteers.

Statistical analysis

Statistical analysis was performed using the Statistica v. 9.0 (StatSoft) and the MedCalc v.12.4.0.0 (MedCalc Software) software. Differences between the evaluated parameters and the upper limit of normal values were evaluated using the Student *t* test for a single sample for normally distributed variables or the signed rank Wilcoxon test for non-normally distributed variables. Relations between levels of conventional and new HF markers were evaluated using the Spearman rank correlation, and the results were expressed graphically using linear regression curves. $P<0.05$ was considered statistically significant.

Results

The mean age in the study group was 63.56 years (range 35–83 years), and men comprised 93% of the study group. Ischemic heart disease was the most common aetiology of HF (53%), and 38 patients were in NYHA class IV. Characteristics of the study group are shown in Table 1.

We found significantly higher median serum BNP and uric acid levels in patients with HF compared to the reference values determined by the test manufacturer (Table 2). Median BNP level in patients with HF was more than 10-fold higher compared to the upper reference limit.

Patients with HF were also found to have significantly higher Ca 125 levels compared to the reference values determined by the test manufacturer (Table 3). Median copeptin level in patients with acute decompensated HF was more than 10-fold higher compared to the control group, a statistically significant difference (Table 3).

Table 1. Study group characteristics

Parameter	Value
Age [years]:	
• mean (range)	63.56 (35–83)
• median (range)	64 (35–83)
Gender, n [%]:	
• men	56 (93)
• women	4 (7)
Aetiology of heart failure, n [%]:	
• ischemic heart disease	32 (53)
• dilated cardiomyopathy	24 (40)
• other	4 (7)
Concomitant conditions, n [%]:	
• hypertension	37 (62)
• diabetes type 2	31 (52)
• hyperlipidaemia	22 (37)
NYHA functional class, n [%]:	
• III	22 (37)
• IV	38 (63)

NYHA — New York Heart Association

Table 2. Conventional heart failure markers in the study group compared to the reference values

Parameter	Study group		Reference values	p
	N	Median (IQR) Mean ± SD		
BNP [pg/mL]	60	1166.50 (636.0–2068.5)	< 100	< 0.0001
Uric acid [mg/dL]	60	9.497 ± 2.426	3–7	< 0.0001

BNP — B-type natriuretic peptide; IQR — interquartile range; SD — standard deviation

The evaluated parameters were not related to age and gender. As a next step, we evaluated correlation between baseline Ca 125 and copeptin levels and BNP and uric acid levels. We found a significant positive correlation between BNP and Ca 125 levels ($r = 0.48$, $p < 0.001$) (Figure 1). Baseline copeptin level was not related to conventional HF markers.

Discussion

Processes that damage myocardium lead to complex hemodynamic disturbances, including volume overload and activation of the renin-angiotensin-aldosterone system and sympathetic system. At the same time, production of natriuretic peptides increases as a compensatory mechanism to cardiac overload [5].

In our study, levels of biochemical parameters and biomarkers of HF were related to normal values. We found significantly higher levels of conventional HF markers such

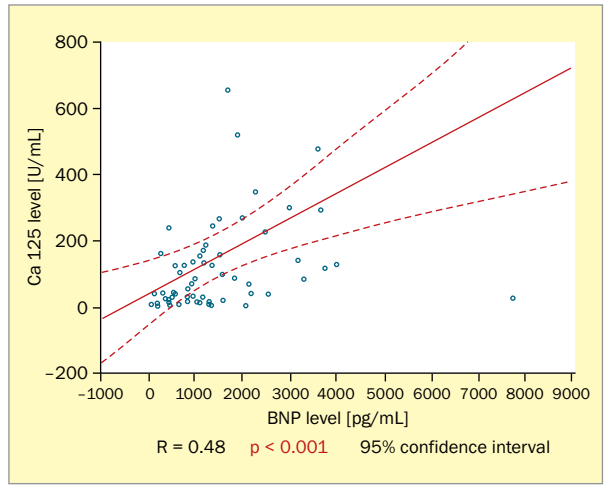

Figure 1. Correlation between B-type natriuretic peptide (BNP) level (pg/mL) and cancer antigen 125 (Ca 125) level (U/mL) in patients with acute decompensated chronic heart failure

Table 3. New biomarkers of heart failure in the study group compared to the reference values

New biomarkers	Study group		Reference values	P
	N	Median (IQR)		
Ca 125 [U/mL]	60	88.71 (29.28–169.00)	0–35	< 0.0001
	Study group		Control group		P
	N	Median (IQR)	N	Median (IQR)	
Copeptin [pg/mL]	60	96.55 (38.85–214.20)	20	7.05 (6.10–13.85)	< 0.0001

Ca 125 — cancer antigen 125; IQR — interquartile range

as BNP and uric acid. These findings are expected in patients with advanced HF who comprised the study group. The role of BNP and uric acid has been well established in numerous studies in patients with HF. High BNP levels are associated with higher NYHA class and worse outcomes [6]. BNP is measured as a screening test to identify asymptomatic patients with left ventricular dysfunction and early HF [7]. Gack et al. [8] showed that plasma BNP levels in patients with HF are very high compared to the normal values (with more than 10-fold increase in severe HF). Similar findings were noted in our study in which the upper limit of the reference range for BNP level was 100 pg/mL and median BNP level in the study group exceeded 1100 pg/mL. Hyperuricemia is a common metabolic abnormality in patients with HF and may predict mortality independent from the severity of cardiac disease. Elevated uric acid levels are seen in 50–55% of patients with systolic HF [9]. Prospective data from 4912 patients in the Framingham Offspring study showed that the incidence of HF was six-fold higher among subjects in the upper quartile of uric acid levels (> 6.3 mg/dL) compared to the lowest quartile (< 3.4 mg/dL) [10].

Our study also showed significantly higher serum levels of two new markers, Ca 125 and copeptin, in patients with acute decompensated HF. In the recent years, a number of reports were published showing elevated Ca 125 levels in HF patients and indicating a possible clinical and biological role of Ca 125 in the complex disease process of HF [11]. In our study, we showed that most patients with acute decompensated NYHA class III or IV HF had elevated baseline Ca 125 level (42 of 60 patients, or 70%). These observations are in agreement with previous literature reports. In a group of 286 patients with systolic HF, D'Aloia et al. [12] showed that Ca 125 level measured on admission was elevated in more than half of their subjects (152 of 286, 53%), mostly with moderate to severe (84% and 100% of patients in NYHA class III and IV, respectively).

Vasopressin is an antidiuretic and vasoconstrictor hormone synthesized in the hypothalamus in response to increased osmolarity and hypovolemia [13]. One study showed that vasopressin level is increased in patients with HF and vasopressin may have an important role in disease progression [14]. Copeptin is a pre-provasopressin fragment synthesized and released in equimolar amounts with vasopressin, and its advantages include stability and possibility of rapid serum or plasma level determination [15]. In our study, we showed that patients with acute decompensated HF had more than 10-fold higher median copeptin level compared to the control group, a statistically significant difference (median 96.5 pg/mL vs. 7.05 pg/mL, or 24.0 pmol/L vs. 1.8 pmol/L, $p < 0.0001$). These findings are similar to other literature data. The upper limit of normal copeptin level in healthy subjects was reported at 11.25–16.4 pmol/L [3]. Other studies also showed an increased copeptin level in patients with HF [16, 17]. Miller et al. [16] reported that median copeptin level in a study in 187 outpatients with NYHA class III–IV HF was 16.6 pmol/L (7.3–31.1) [16]. Similarly, in a study by Balling et al. [17], median copeptin level in outpatients with NYHA class I–IV HF was 15.5 pmol/L (5.60–54.82). In another study in 786 patients with NYHA class I–IV HF, mean copeptin level was elevated at 18.9 ± 24.2 pmol/L (range 0.7–224 pmol/L) [18]. Voors et al. [19] studied copeptin level in patients 3 days after an acute myocardial infarction, all with symptoms of HF and a reduced left ventricular ejection fraction below 35%. Despite very short duration of HF, copeptin levels were already elevated (median 14 pmol/L, range 8–26 pmol/L). It was also found that copeptin level decreased at one year (median 7 pmol/L, range 5–11 pmol/L), which may indicate a high sensitivity of this diagnostic test.

Our findings indicated a significant positive relation between baseline BNP and Ca 125 levels in the study group ($r = 0.48$, $p < 0.001$). Similar results were reported by Duman et al. in patients with NYHA class III–IV HF, in whom elevated Ca 125 levels were observed in parallel to an increase in norepinephrine and particularly BNP levels [20]. Chen et al. showed that in patients with HF, BNP and Ca 125 levels were significantly higher compared to subjects without HF, and Ca 125 level showed a positive correlation with the left ventricular ejection fraction ($r = 0.789$, $p < 0.01$), similarly to BNP ($r = 0.730$, $p < 0.01$) [21]. In another study in 293 patients admitted due to acute decompensated HF, the prognostic value of BNP and Ca 125 was evaluated. The endpoint included death and hospitalization due to exacerbation of HF, and the median duration of follow-up was 18 months. The authors showed a superior prognostic value of the combination of both markers, BNP and Ca 125 [22]. Folga et al. [23] showed that elevated NT-proBNP and Ca 125 levels are independent predictors of mortality in patients with HF.

Available literature data indicate that these two biomarkers reflect different pathophysiological mechanisms associated with exacerbation of HF. The mechanism of elevation of serum Ca 125 level in patients with acute decompensated HF has not been clearly elucidated. Some authors have suggested that it may be related to pleural, peritoneal, and pericardial effusion [11]. High Ca 125 levels may be associated with volume overload and inflammation [24]. Indirect evidence that elevated Ca 125 levels in patients with HF are not only related to volume overload was provided by the study by D'Aloia et al. who showed that an increase in Ca 125 level was seen both in patients with effusion and those without effusion [12]. A similar relation was reported by Nagele et al. [25]. Another study showed a significant relation between Ca 125 level and

left ventricular end-diastolic pressure and BNP level, the latter being produced mainly in response to increase left ventricular wall strain and volume overload [11]. Based on these studies, it may be suggested that production of Ca 125 in patients with HF may have complex aetiology and may show relation with increased BNP level. Another advantage of evaluating both markers may be their different pharmacokinetics. BNP has a short half-life (20 minutes) while Ca 125 is a stable marker with a half-life of more than one week. Based on the above results, it may be suggested that Ca 125 reflects changes in volume status and inflammation while BN reflects transient hemodynamic changes in patients with HF.

No relation was found between baseline copeptin levels and conventional markers of HF. Multiple studies showing the predictive value of copeptin in patients with HF are available in the literature, while few studies evaluated the relation between copeptin and BNP levels. One study showed, using logistic regression analysis, a weak correlation between copeptin and NT-proBNP levels in 340 patients with NYHA class III–IV HF [26]. Our finding of no relation between copeptin and BNP levels may be perhaps explained by a smaller sample evaluated in our study compared to the above cited study.

Several limitations of our study should be noted in relation to the available literature data. First, our study was smaller than studies reported by other authors. We only evaluated patients with severe heart failure (NYHA class III–IV). The study group consisted mostly of men, similarly to studies by other authors, while registries indicate an increasing incidence and prevalence of HF in women [27]. In the study by Maedy et al. [28], measurements of HF biomarkers at 3 months after hospital discharge had an additional prognostic value . In our study, last measurement of the study parameters were performed at discharge. However, our findings should prompt further studies in a larger patient population with a longer follow-up and outpatient measurement of biomarker levels.

Conclusions

1. In patients with acute decompensated HF, baseline Ca 125 and copeptin levels were significantly elevated compared to the reference values and control group, respectively. 2. Despite different pathomechanisms of BNP and Ca 125 level elevations, a correlation was found between these markers, which might indicate a complex pathophysiology of HF.

Streszczenie

Wstęp. Wciąż poszukuje się nowych markerów sercowych i nowych metod monitorowania, które mogą być użyteczne w terapii chorych z zaawansowaną niewydolnością serca (HF). W ostatnich doniesieniach naukowych wykazano, że u pacjentów z HF obserwuje się podwyższone stężenia antygenu nowotworowego 125 (Ca 125) oraz kopeptyny, co może sugerować, że substancje te są markerami HF.

Materiał i metody. Celem badania była ocena stężenia potencjalnych markerów HF w odniesieniu do klasycznych, biochemicznych czynników rokowniczych. Do badania włączono 60 pacjentów z zaostrzeniem przewlekłej HF w III i IV klasie czynnościowej według *New York Heart Association*. Przy przyjęciu do szpitala pobierano krew w celu oznaczenia stężeń klasycznych czynników rokowniczych (kwas moczowy, peptyd natriuretycznego typu B [BNP]) oraz nowych biomarkerów — Ca 125 i kopeptyny.

Wyniki. W badanej grupie wykazano istotnie statystycznie podwyższone stężenia klasycznych markerów HF takich jak BNP (Me: 1166,50 pg/ml [636,00–2068,50]) oraz kwas moczowy (X: 9,497 ± 2,426) w stosunku do wartości prawidłowych. W przypadku nowych markerów HF stwierdzono, że stężenie Ca 125 w badanej grupie również było istotnie podwyższone w odniesieniu do wartości prawidłowych (Me: 88,71 [29,28–169,00]). Stężenie kopeptyny w badanej grupie było istotnie wyższe niż w grupie kontrolnej (Me: 96,55 pg/ml *v.* 7,05; $p < 0,0001$). Ponadto zaobserwowano statystycznie znamienną współzależność między wyjściowymi stężeniami BNP i Ca 125 ($R = 0,48$; $p < 0,001$). Nie wykazano współzależności między wyjściowymi stężeniami kopeptyny a stężeniami klasycznych markerów HF — BNP i kwasu moczowego.

Wnioski. W zaawansowanej HF dochodzi do zaburzeń wielu patomechanizmów, co ma odzwierciedlenie w podwyższonych stężeniach różnych substancji, zarówno klasycznych, jak i nowych markerów HF. Podwyższone wartości Ca 125 obserwuje się u chorych z ciężką HF mimo braku choroby nowotworowej, jednak Ca 125, ze względu na małą swoistość, nie przewyższa prognostycznie wartości stężeń BNP. Mimo odmiennego patomechanizmu stężenia BNP oraz Ca 125 wykazywały współzależność, co może świadczyć o złożonej patofizjologii HF w badanej grupie.

Słowa kluczowe: niewydolność serca, biomarkery, Ca 125, kopeptyna, BNP

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