

Evaluation of the clinical utility of urocortin 1 in systolic heart failure

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Abstract

Background: Urocortin 1 (UCN1) has cardiostimulatory, vasodilatory, diuretic and natriuretic effects, and its expression increases in heart failure (HF).

Aim: To determine UCN1 levels in patients with HF, to evaluate UCN1's relationship with various clinical parameters, and to assess UCN1 as a diagnostic marker in HF, compared to pro-B-type natriuretic peptide (pro-BNP).

Methods: We investigated serum levels of UCN1 and pro-BNP in 90 consecutive patients with systolic HF (left ventricular ejection fraction [LVEF] ≤ 45%) and 90 healthy controls. Serum UCN1 and pro-BNP levels were measured using the ELISA method. Transthoracic echocardiography was performed to determine LVEF and pulmonary artery systolic pressure (PASP). Glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault formula.

Results: UCN1 level was higher in HF patients (391.5 [357.0–482.0] pg/mL, $p < 0.001$). UCN1 was positively related with NYHA class ($r = 0.89$, $p < 0.001$), and PASP ($r = 0.39$, $p < 0.001$); and negatively related with LVEF ($r = -0.46$, $p < 0.001$), and GFR ($r = -0.21$, $p = 0.046$). A significant positive correlation was found between pro-BNP and UCN1 levels ($p < 0.001$, $r = 0.96$). Receiver operating characteristic (ROC) curves yielded an area under the curve (AUC) of 0.99 (95% CI 0.98–1.00, $p < 0.001$) for UCN1 and 1.00 ($p < 0.001$) for pro-BNP in the diagnosis of HF.

Conclusions: UCN1 increases with worsening HF and left ventricular dysfunction. It may be used as a diagnostic biomarker in systolic HF, but the incremental value of measuring UCN1 in patients tested for pro-BNP is questionable.

Key words: urocortin 1, heart failure, pro-B-type natriuretic peptide, diagnosis

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INTRODUCTION

Urocortins are peptides consisting of 40 amino acids and they belong to the family of corticotrophin releasing factors (CRF). They are novel cardiovascular peptides which are named after their homologies with fish urotensin and mammalian CRF [1]. Peptides making up the CRF family act via two CRF receptors which are coded by two different genes: CRF type 1 and type 2 receptors [2–6]. Besides the first described urocortin (urocortin 1), there are two other peptides in this family, namely urocortin 2 and 3 [7]. The homology between urocortins 2, 3, CRF and urocortin 1 is within the range of 20–40% [2, 3, 8]. The gene for urocortin 1 is found in chromosome 2p23-2p21 and encodes a 123 amino acid precursor [7]. In humans, urocortin 1 is detected in the brain, placenta,

gastro-intestinal tract, synovial tissue, lymphocytes, adipose tissue, endothelial cells, immune tissues and heart [9–15]. Urocortin 1 is known to act through CRF type 1 receptor [16]. Via this receptor, it has been demonstrated to increase anxiety and suppress appetite [7]. In animal studies, urocortin has triggered hypophyseal-adrenal axis causing ACTH secretion, and increased the plasma levels of plasma cortisol and atrial natriuretic peptide. In humans, the administration of urocortin 1 to healthy male subjects has resulted in increased plasma ACTH and cortisol levels [17–20]. Urocortin's anti-inflammatory and antioxidative effects have been shown in terms of reduction of lipopolysaccharide-induced tumour necrosis factor alpha release in *in vivo* and *in vitro* studies [21, 22].

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The effects of urocortins on cardiac physiology have been demonstrated in healthy animals, as well as in pacemaker induced animal heart failure (HF) models [19–24]. Urocortins increase heart rate and cardiac output and coronary blood flow in a dose related manner [19, 25]. In cardiac cells other than myocytes, they increase collagen and DNA synthesis [26]. Interestingly, urocortins have been shown to display anti-apoptotic effects on myocardial tissue jeopardised with ischaemia-reperfusion injury, through a process mediated via mitogen activated protein kinase [19, 23, 24]. In rats, urocortin 1 increases cardiac contractility and heart rate and induces vasodilatation, as well as natriuresis/diuresis [20–26]; however, these effects cannot be observed in rats lacking CRF type 2 receptors [26, 27]. Urocortin 1 has also been demonstrated to decrease peripheral vascular resistance and left atrial pressure [20–33].

Clinical studies investigating the role of urocortin in HF patients are limited. In a study by Ng et al. [34], plasma urocortin levels were demonstrated to be higher in systolic HF patients compared to healthy controls, which was more pronounced in males. In this study, urocortin fell with increasing age, especially in systolic HF patients. Urocortin levels decreased with increasing New York Heart Association (NYHA) class. The authors suggested that urocortin measurement might complement N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the diagnosis of early HF. They also speculated that the role of urocortin administration in the treatment of HF remained to be explored. Wright et al. [35] investigated the utility of plasma urocortin 1 measurement in the diagnosis of HF and demonstrated that, in patients with recent onset dyspnoea and HF, urocortin 1 increased in proportion to the degree of cardiac dysfunction and worsening functional status, in contrast to the findings of Ng et al. [34].

The aim of this study was to determine serum urocortin 1 levels in patients with HF and to evaluate urocortin 1's relationship with important clinical parameters such as NYHA class, left ventricular ejection fraction (LVEF), pulmonary artery systolic pressure (PASP), pro-BNP level and renal function in terms of glomerular filtration rate (GFR). We also aimed to evaluate urocortin 1 as a diagnostic marker in patients with heart failure, compared to pro-BNP.

METHODS

In this study, 90 consecutive patients admitted to the outpatient cardiology clinic of a university hospital with compensated or decompensated systolic HF (LVEF \leq 45%), and 90 healthy controls, were enrolled. Diagnosis of HF was made according to the 2012 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure criteria [36]. The functional status of each patient was determined in terms of NYHA class. Patients' past medical histories were recorded including concomitant diseases and medical therapies used for the treatment of HF. Exclusion criteria consisted of hospitalisa-

tion for acute coronary syndromes, HF with preserved LVEF ($>$ 45%), history of any neoplastic, inflammatory, infectious, and connective tissue disease, acute renal failure, hepatic failure, recent trauma or major surgery, and pregnancy. All subjects underwent transthoracic echocardiographic examination (Vivid 3, General Electric, Milwaukee, WI, USA) performed by an experienced operator in order to determine LVEF, and PASP values. LVEF was determined using Simpson's method of discs in two-dimensional echocardiography and PASP was estimated from the velocity of regurgitant tricuspid jets. GFR of each subject was estimated using the Cockcroft-Gault formula to assess renal functions. After echocardiographic examination, 5 mL of blood was collected in the supine position, after 10 min of bed rest, into tubes containing EDTA and aprotinin. Serum was stored at -80°C until assayed. Serum urocortin 1 levels were measured using commercially available ELISA kits (Phoenix Pharmaceuticals, USA). The cross-reactivities documented for the urocortin assay by the manufacturer are 100% with human urocortin 1 and 0% with human urocortin 2, human urocortin 3 and human CRF. The intra-assay coefficient of variation (CV) was 6% for a concentration of 100 pmol/L and the inter-assay CV was 12% for the same concentration. The lower limit of quantification of the assay was determined to be 20 pmol/L. Serum pro-BNP levels were measured using commercially available kits (Phoenix Pharmaceuticals, USA). All patients were above 18 years of age and able to provide written informed consent, which was a prerequisite for enrollment. This study complies with the Declaration of Helsinki and trial protocol was approved by the local Ethics Committee.

Statistical analysis

The values were expressed as mean \pm standard deviation (SD) or the median and the interquartile range (IQR, range from the 25th to the 75th percentile). We used Pearson test for correlations. Differences of continuous and categorical variables between two groups were studied using the independent samples Student t or Mann-Whitney U tests. Associations between categorical variables were evaluated using the χ^2 or Fisher's Exact tests. The Spearman correlation coefficient was calculated for the comparison of two data sets. Diagnostic values were determined with receiver operating characteristic (ROC) analysis. A p value $<$ 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS version 16 (SPSS for Windows, Version 16.0. SPSS Inc., Chicago, IL, USA).

RESULTS

The demographic properties of the study and control groups are given in Table 1. The mean age of the study group was significantly higher than the control group. The percentage of men was significantly higher among HF patients compared to controls.

Table 1. Baseline demographic, clinical and laboratory characteristics of the patient and control groups

	Patient (n = 90)	Control (n = 90)	P
Age [years]	64.82 ± 12.14	34.83 ± 11.55	< 0.001
Gender: male	66.7%	38.9%	< 0.001
Ejection fraction [%]	32.2 ± 6.9	60 ± 3.3	< 0.001
Pulmonary artery systolic pressure [mm Hg]	41.1 ± 9.2	20 ± 4.8	< 0.001
Haemoglobin [g/dL]	11.9 ± 1.9	12.7 ± 2.1	< 0.015
Haematocrit [%]	36.3 ± 5.5	38.2 ± 7	0.04
Glycated haemoglobin A1c [%]	6.4 ± 0.8	5.7 ± 0.1	< 0.001
Glomerular filtration rate [mL/min]	65.3 ± 25.2	112.2 ± 14.4	< 0.001
pro-BNP (IQR) [pg/mL]	4910.5 (3749.0–9837.0)	298.0 (280.0–359.0)	< 0.001
Urocortin (IQR) [pg/mL]	391.5 (357.0–482.0)	109.0 (102.0–158.0)	< 0.001

pro-BNP — pro-B-type natriuretic peptide; IQR — interquartile range

The distribution of patients according to their NYHA class was as follows: 54.4% NYHA II, 37.8% NYHA III, and 7.8% NYHA IV. When patients were evaluated according to the aetiology of HF, the most frequent cause was ischaemia (64.4%), followed by idiopathic dilated cardiomyopathy (16.7%), hypertension (12.2%), diabetes (2%) and valvular heart disease (3.3%). Chronic diseases accompanying HF in the study group were coronary artery disease (63.3%), hypertension (58.9%), diabetes mellitus (32.2%), chronic renal disease (30%) and atrial fibrillation (32.2%). Therapy for HF included beta-blockers (76.7%), furosemide (71.1%), angiotensin converting enzyme (ACE) inhibitors (47.8%), angiotensin receptor blockers (ARB) (20%), spironolactone (25.6%), and digoxin (16.7%).

The mean LVEF was 32.2 ± 6.9% in the patient group, and 60 ± 3.3% in the control group ($p < 0.001$). As expected, the LVEF was lower in the patient group compared to controls. PASP was significantly higher in the patient group compared to controls (41.1 ± 9.2 vs. 20 ± 4.8 mm Hg; $p < 0.001$).

Urocortin 1 and pro-BNP levels were compared in terms of their diagnostic ability of HF using ROC analysis. At the level of 250 pg/mL, urocortin 1 had 97.8% sensitivity and 100% specificity. Area under the curve (AUC) was 0.99 (95% confidence interval [CI] 0.98–1.00, $p < 0.001$). Pro-BNP had a sensitivity and specificity of 100% at the level of 1,000 pg/mL; AUC for pro-BNP was 1.00 ($p < 0.001$) (Fig. 1).

When the prognostic variables of HF were examined, the median level of pro-BNP was found to be 4910.5 (IQR 3749.0–9837.0) pg/mL in HF patients and 298.0 (IQR 280.0–359.0) pg/mL in the control group ($p < 0.001$). The median urocortin 1 level was significantly higher than that of the healthy subjects (391.5 [357.0–482.0]) pg/mL vs. 109.0 [102.0–158.0] pg/mL; $p < 0.001$. A significant correlation was found between pro-BNP and urocortin 1 levels ($p < 0.001$, $r = 0.96$) in patients with HF (Fig. 2).

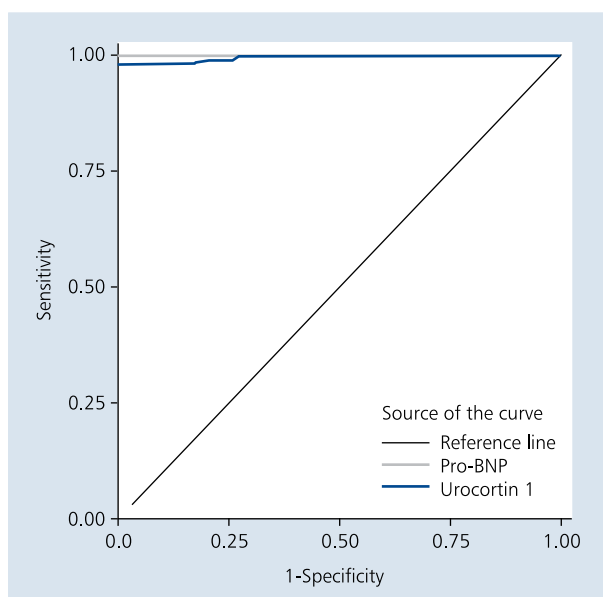


Figure 1. A comparison of urocortin 1 and pro-B-type natriuretic peptide (pro-BNP) levels using receiver operation curve (ROC) analysis

In the patient group, a highly significant positive correlation was demonstrated between NYHA class and urocortin 1 levels ($p < 0.001$, $r = 0.896$) (Fig. 3). Systolic HF patients were categorised into two groups according to their NYHA functional class in order to assess and compare the median level of urocortin 1 in different clinical status. While group 1 consisted of stable chronic HF patients (NYHA I–II) ($n = 49$), group 2 consisted of decompensated HF (NYHA III–IV) ($n = 41$). The median level of urocortin was found to be significantly higher in patients with NYHA III–IV than in patients with NYHA I–II (Group 1 vs. Group 2 (median 360.0, IQR 345.0–376.0 pg/mL vs. median 485.0, IQR 465.0–496.0 pg/mL, $p < 0.001$).

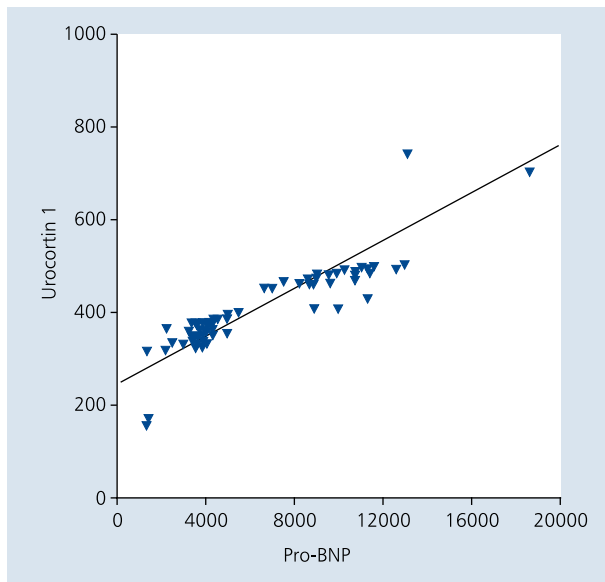


Figure 2. A correlation between pro-B-type natriuretic peptide (pro-BNP) and urocortin 1 level

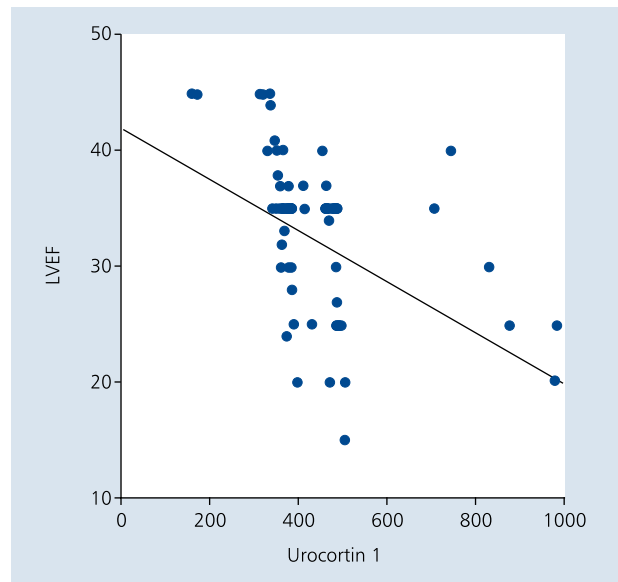


Figure 4. A correlation between left ventricular ejection fraction (LVEF) and urocortin 1 level

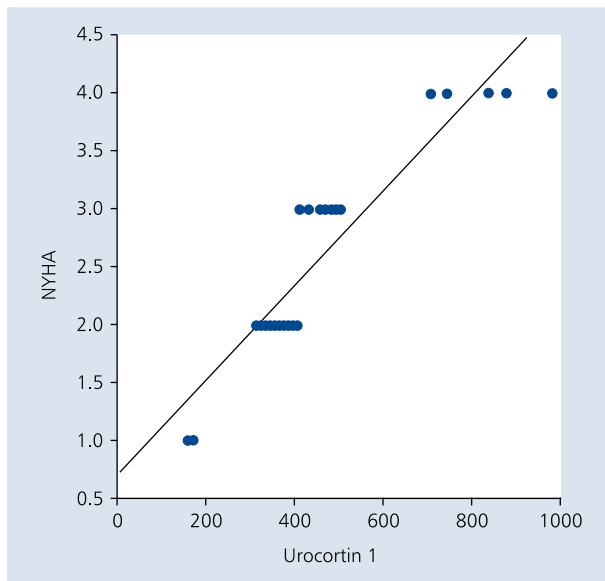


Figure 3. A correlation between New York Heart Association (NYHA) class and urocortin 1 level

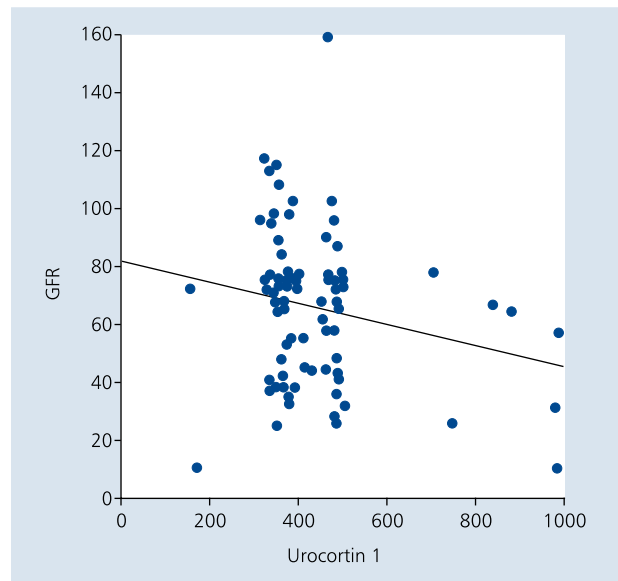


Figure 5. A correlation between glomerular filtration rate (GFR) and urocortin 1 level

Furthermore, urocortin 1 levels were inversely correlated with LVEF in HF patients ($p < 0.001$, $r = -0.46$) (Fig. 4). When the relation between urocortin 1 levels and PASP was investigated, a significant positive correlation was found ($p < 0.001$, $r = 0.39$).

Due to the well documented relation between renal function and prognosis in HF patients, the association between urocortin 1 and GFR was evaluated. Urocortin 1 levels increased as GFR decreased ($p = 0.046$, $r = -0.21$) (Fig. 5).

We were unable to demonstrate any correlation between urocortin 1 levels and either age or sex in all subjects.

DISCUSSION

The physiological functions of urocortins in healthy humans and their roles in various pathophysiological states constitute a subject of active investigation. Urocortins are known to exhibit various effects on the cardiovascular system including increased heart rate, cardiac output, and coronary blood flow.

They also induce natriuresis, diuresis, and positive inotropy. Urocortins also display myocardial cardioprotective and anti-inflammatory effects [21, 23].

The role of urocortins in the pathophysiology of systolic HF has been investigated in previous studies. Ng et al. [34] studied the plasma levels of urocortin in patients with systolic HF. They found increased urocortin levels in HF patients compared to healthy controls. This increase was relatively larger in males, and levels decreased along with increasing age in patients with HF. Although urocortin levels were higher in HF patients, they were lower in the NYHA class III–IV group compared to the NYHA class I–II group. Wright et al. [35] and Gruson et al. [37] investigated plasma levels of urocortin 1 in HF patients. They, just like our study, showed that urocortin 1 levels increase with increasing NYHA class, from I to IV. They also could not demonstrate any relationships between age, sex and urocortin 1 levels, just as is the case in this study.

The relation between LVEF and urocortin levels has been investigated in various clinical studies. Ng et al. [34] reported an inverse correlation between urocortin levels and LVEF with lower values of urocortin in patients in lower LVEF quartiles. On the other hand, Wright et al. [35] and Gruson et al. [37] demonstrated plasma urocortin 1 levels to increase with decreasing LVEF. We were able to replicate their results. The disparity between the study of Ng et al. [34] and the other investigators, including our results, warrants some attention. The answers may lie within the differing characteristics of the immunoassays used, as suggested by Wright et al. [35]. We used a commercially available ELISA kit, as in the study by Gruson et al. [37]. In addition to the echocardiographic parameters investigated in the aforementioned studies, we examined the relationship between PASP and urocortin 1 levels. We managed to demonstrate a positive correlation between PASP values and levels of urocortin 1.

The relationships between urocortins and natriuretic peptides, established diagnostic and prognostic biomarkers in HF, were investigated in recent clinical studies. Ng et al. [34] demonstrated a negative correlation between urocortin levels and NT-BNP, while Wright et al. [35] reported a positive correlation between urocortin 1 and NT-BNP, as well as BNP, adrenomedullin, endothelin 1, and C type natriuretic peptide. We have found a positive relation between urocortin 1 levels and plasma pro-BNP levels, like Wright et al. [35].

The relation between another prognostic factor in HF patients, namely renal function, and urocortin 1 levels, was assessed by Wright et al. [35]. They demonstrated an inverse correlation between GFR levels and urocortin 1. In our study, a similar relation between GFR and urocortin 1 was observed.

The diagnostic utility of urocortin 1 and NT-BNP levels in patients with HF has been evaluated previously [35–38]. Ng et al. [34] demonstrated increased sensitivity and specificity with the addition of urocortin measurement to NT-BNP testing, in the diagnosis of HF [34]. On the other hand, Wright et al. [35]

reported a lower diagnostic ability of urocortin 1, compared to NT-BNP (AUC of urocortin 1 and NT-BNP = 0.68 [95% CI 0.61–0.75, $p < 0.001$] and 0.85 [95% CI 0.80–0.90, $p < 0.0001$], respectively). In this study, using ROC analysis, urocortin 1 was demonstrated to display a slightly weaker performance compared to pro-BNP in the diagnosis of HF (AUC of urocortin 1 and NT-BNP = 0.99 [95% CI 0.98–1.00, $p < 0.001$] and 1.00 [$p < 0.001$], respectively).

Limitations of the study

The absence of a sex- and age-matched control group was one limitation of our study. However, the fact that we were unable to demonstrate any correlation between age, sex and urocortin 1 levels in the study group, like Wright et al. [25], must also be taken into account. Since urocortin 1 levels were measured only once during admission, we could not evaluate the changes in urocortin 1 concentrations in response to treatment due to lack of serial measurements. Also, the lack of comparison and discussion between urocortin 1 and BNP/NT-proBNP was another limitation of the study. The lack of evaluation of the prognostic role of urocortin 1 in systolic HF due to cross-sectional design was the final limitation of the present study.

CONCLUSIONS

The findings of this study suggest that urocortin 1 may be used as a diagnostic biomarker in systolic HF, but the incremental value of measuring urocortin 1 when considered in patients tested for pro-BNP levels is questionable. We have demonstrated urocortin 1 levels to increase with worsening HF, as demonstrated by its positive correlation with NYHA class, pro-BNP, PASP, and its negative correlation with LVEF and GFR.

The significance of the inverse relationship between GFR and urocortin 1 levels needs to be studied further. Also, the role of urocortin 1 in the initial diagnosis of diastolic HF, along with its possible contribution to the estimation of prognosis of systolic and diastolic HF, needs to be clarified with further studies.

Conflict of interest: none declared

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Ocena klinicznego zastosowania stężenia urokortyny 1 w skurczowej niewydolności serca

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Streszczenie

Wstęp: Urokortyna 1 (UCN1) ma działanie kardiostymulujące, diuretyczne i natriuretyczne, a jej ekspresja zwiększa się w niewydolności serca (HF).

Cel: Celem niniejszego badania były: ocena stężeń UCN1 u chorych z HF, ocena związku UCN1 z różnymi parametrami klinicznymi oraz ocena przydatności UCN1 jako wskaźnika diagnostycznego HF w porównaniu z peptydem natriuretycznym typu B (pro-BNP).

Metody: Autorzy zmierzili stężenia UCN1 i pro-BNP w surowicy u 90 kolejnych pacjentów ze skurczową HF (frakcja wyrzutowa lewej komory [LVEF] ≤ 45%) i u 90 zdrowych osób stanowiących grupę kontrolną. Do pomiaru stężeń UCN1 i pro-BNP w surowicy użyto metody ELISA. W celu określenia LVEF i ciśnienia skurczowego w tętnicy płucnej (PASP) przeprowadzono przezprzetykowe badanie echokardiograficzne. Ponadto oszacowano filtrację kłębuszkową (GFR), stosując wzór Cockcrofta-Gaulta.

Wyniki: Stężenie UCN1 było wyższe u chorych z HF (391,5 [357,0–482,0] pg/ml; $p < 0,001$). Stwierdzono dodatnią korelację stężenia UCN1 z klasą NYHA ($r = 0,89$; $p < 0,001$) i PASP ($r = 0,39$; $p < 0,001$) oraz ujemną korelację z LVEF ($r = -0,46$; $p < 0,001$) i GFR ($r = -0,21$; $p = 0,046$). Zanotowano również istotną dodatnią zależność między stężeniami pro-BNP i UCN1 ($p < 0,001$; $r = 0,96$). W celu oceny wartości parametrów w diagnozowaniu HF wyznaczono krzywe ROC i obliczono pole pod krzywą (AUC), które wynosiło 0,99 (95% CI 0,98–1,00; $p < 0,001$) w przypadku stężenia UCN1 oraz 1,00 ($p < 0,001$) w przypadku stężenia pro-BNP.

Wnioski: Stężenie UCN1 zwiększa się w miarę nasilania się HF i dysfunkcji lewej komory. Parametr ten może być stosowany jako diagnostyczny biomarker w skurczowej HF, jednak znaczenie pomiaru UCN1 jako badania uzupełniającego u pacjentów, u których wykonano oznaczenie pro-BNP, jest wątpliwe.

Słowa kluczowe: urokortyna 1, niewydolność serca, czynnik natriuretyczny typu B, rozpoznanie

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