The evaluation of the clinical utility of urocortin 1 and adrenomedullin versus proBNP in systolic heart failure

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ABSTRACT

Objective: Urocortin 1 (UCN1) has vasodilator, diuretic, and natriuretic effects, and its expression increases in heart failure (HF). Adrenomedullin (ADM) increases cardiac output and lowers blood pressure in healthy men and in patients with heart failure. The aim of the study was to determine UCN1 and ADM levels in patients with HF, to evaluate the relationship of UCN1 and ADM with various clinical parameters, and to assess UCN1 and ADM as diagnostic markers in HF, in comparison with pro-brain natriuretic peptide (pro-BNP).

Methods: We investigated serum levels of UCN1, ADM, and pro-BNP in 86 consecutive patients with systolic HF [ejection fraction (EF) ≤45%] and 85 healthy controls. Serum UCN1, ADM, and pro-BNP levels were measured with the ELISA method. Transthoracic echocardiography was performed to determine left ventricular EF and pulmonary artery systolic pressure.

Results: UCN1 and ADM levels were higher in HF patients (446.2±145.7 pg/mL, p<0.001; 87.9±4.2 pg/mL, p<0.001 respectively). UCN1 was positively correlated with pro-BNP (r=0.963, p<0.001), ADM (r=0.915, p<0.001), and NYHA (r=0.879, p<0.001); ADM was positively correlated with pro-BNP (r=0.956, p<0.001) and NYHA (r=0.944, p<0.001). Receiver operating characteristic curves yielded an area under the curve of 1.00 (p<0.001) for UCN1, 1.00 (p<0.001) for ADM, and 0.99 (p<0.001) for pro-BNP in the diagnosis of HF.

Conclusion: UCN1 and ADM increase with worsening HF and left ventricular dysfunction. They may be used as diagnostic biomarkers in systolic HF, but the incremental value of measuring UCN1 and ADM in patients tested for pro-BNP is questionable.

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Key words: urocortin 1, adrenomedullin, heart failure, pro-brain natriuretic peptide

Introduction

A wide range of cardiovascular disorders that result in the impairment of the heart's ability to pump out blood may eventually lead to the clinical syndrome of heart failure (HF). In recognition of the multiplicity of causes of the diagnosis, it is not surprising that HF is a common affliction. Currently, an estimated 23 million people worldwide are living with HF (1). As the population ages and treatments for cardiovascular diseases are improving mortality in affected patients, the number of HF patients is expected to grow. HF biomarkers have dramatically impacted the way HF patients are evaluated and managed. B-type natriuretic peptide (BNP) and N-terminal proBNP are the gold standard biomarkers in determining the diagnosis and prognosis of HF. An array of additional biomarkers has emerged, each reflecting different pathophysiological processes in the development and progression of HF: myocardial insult, inflammation, and remodeling.

Urocortins are peptides consisting of 40 amino acids, and they belong to the family of corticotropin-releasing factors (CRFs). They are novel cardiovascular peptides that are named after their homology with fish urotensin and mammalian CRF (2). Besides the first described urocortin (urocortin 1), there are two other peptides in this family, namely urocortin 2 and 3 (3). In humans, urocortin 1 (UCN1) is detected in the brain, placenta, gastro-intestinal tract, synovial tissue, lymphocytes, adipose tissue, endothelial cells, immune tissues, and heart (4-10). In animal studies, urocortin has triggered the hypophyseal-adrenal axis, causing ACTH secretion, and increased the plasma levels of plasma cortisol and atrial natriuretic peptide (ANP). In humans, administration of UCN1 to healthy male subjects has resulted in increased plasma ACTH and cortisol

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levels (11-14). Urocortin's anti-inflammatory and antioxidative effects were shown in terms of a reduction of lipopolysaccharide-induced tumor necrosis factor α release in in vivo and in vitro studies (15, 16). Urocortins increase heart rate, cardiac output, and coronary blood flow in a dose-related manner (13, 17). Urocortins have been shown to display anti-apoptotic effects on myocardial tissue that has been jeopardized by ischemia-reperfusion injury, through a process mediated via mitogen-activated protein kinase (13, 18, 19). In rats, UCN1 increases cardiac contractility and heart rate and induces vasodilatation, as well as natriuresis/diuresis (14-20). UCN1 has also been demonstrated to decrease peripheral vascular resistance and left atrial pressure (14-27).

Adrenomedullin (ADM) was discovered in human pheochromocytoma tissue and was subsequently found to be a circulating hormone. ADM is released from the vascular wall and acts as an autocrine or a paracrine hormone to regulate vascular tone and blood pressure. It is a powerful vasodilator and reduces blood pressure. The biological activity of ADM is exerted through the calcitonin receptor-like receptor and a specific receptor activity-modifying protein. ADM binds to these receptor complexes and activates the second messenger signal, resulting in an increase in cAMP and nitric oxide synthesis. ADM also plays a significant role in various pathological conditions, including hypertension, myocardial infarction, and heart failure. Systemic administration of ADM increases cardiac output and lowers blood pressure in healthy men and in patients with heart failure (28). The increase in cardiac output can be explained by various mechanisms, including a decrease in systemic vascular resistance and an increase in coronary flow due to coronary vessel dilation. ADM activates protein kinase A and, so, augments myocardial contractility. Besides, it can exert a positive inotropic effect on myocardial cells by a cAMP-independent mechanism in which the intracellular calcium level is increased (29).

Clinical studies investigating the role of UCN1 and ADM in heart failure patients are limited. Ng et al. (30) demonstrated that plasma UCN1 levels were higher in systolic HF patients compared to healthy controls, which were more pronounced in males. Wright et al. (31) showed that ADM increases with increasing severity of symptoms and cardiac dysfunction and rises in parallel with other neurohormonal markers, including the natriuretic peptides and endothelin 1.

The aim of this study was to determine serum UCN1 and ADM levels in patients with heart failure and to evaluate the relationship of UCN1 and ADM with important clinical parameters, such as NYHA class, left ventricular ejection fraction (EF), pulmonary artery systolic pressure (PASP), pro-brain natriuretic peptide (proBNP) level, and renal function in terms of glomerular filtration rate (GFR). We also aimed to evaluate UCN1 and ADM as diagnostic markers in patients with heart failure, in comparison with proBNP.

Methods

Informed consent

The protocol for sample collection was approved by the İstanbul University, Cerrahpasa Medicine Faculty Ethics Committee and was carried out according to the requirements of the Declaration of Helsinki. All patients were fully informed of the study procedures before they gave their consent.

Study population

Study design

This study was designed as a cross sectional observational study.

In this study, 86 consecutive patients, admitted to the outpatient cardiology clinic of a university hospital with compensated or decompensated systolic heart failure [ejection fraction (EF) ≤45%], and 85 healthy controls were enrolled. Diagnosis of heart failure was made according to the 2012 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure (32). The functional status of each patient was determined in terms of NYHA class. The distribution of patients according to their NYHA class was as follows: 1.2% NYHA I, 51.2% NYHA II, 39.5% NYHA III, and 8.1% NYHA IV. When patients were evaluated according to the etiology of heart failure, the most frequent cause was ischemia (62.8%), followed by idiopathic dilated cardiomyopathy (17.4%), hypertension (12.8%), diabetes (2.3%), and valvular heart disease (3.5%). Chronic diseases accompanying heart failure in the study group were coronary artery disease (61.6%), hypertension (58.1%), diabetes mellitus (29.1%), chronic renal disease (31.4%), and atrial fibrillation (33.7%). Patients' past medical histories were recorded, including concomitant diseases and medical therapies used for treatment of heart failure. Therapy for heart failure included beta-blockers (76.7%), furosemide (74.4%), angiotensin-converting enzyme (ACE) inhibitors (48.8%), angiotensin receptor blockers (ARBs) (18.6%), spironolactone (26.7%), and digoxin (17.4%). Exclusion criteria consisted of hospitalization for acute coronary syndromes; heart failure with preserved EF (>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 a trans-thoracic echocardiographic examination (Vivid 3, General Electric, Milwaukee, Wisconsin, USA), performed by an experienced operator, in order to determine EF and PASP values. EF was determined using Simpson's method of discs by 2-dimensional echocardiography, and PASP was estimated from the velocity of regurgitant tricuspid jets. The glomerular filtration rate of each subject was estimated using the Cockcroft-Gault formula to assess renal functions.

Sample collection and measurements

Blood samples were collected after the echocardiographic examination and fasting in the morning in EDTA- and aprotinin-

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Table 1. Demographic characteristics and clinic and laboratory characteristics of the patient and control groups

	Control group (n=85)	Patient group (n=86)	P
Gender, F/M	46/39	38/48	0.194
Age, years	60.1±6.3	62.5±10.5	0.075
EF, %	60.1±3.4	31.8±6.8	<0.001
PASP, mm Hg	20.1±4.8	41.8±9.3	<0.001
Hbg, g/dL	12.8±2.1	11.9±1.9	0.005
Hct, %	38.2±7.1	36.2±5.6	0.035
HbA1c, %	5.72±0.2	6.4±0.8	<0.001
GFR, mL/min	112.2±14.3	64.3±25.1	<0.001
ProBNP, pg/mL	315±50	7669±5557	<0.001
Urocortin 1, pg/mL	126.6±32.7	446.2±145.7	<0.001
Adrenomedullin, pg/mL	70.4±3.1	87.9±4.2	<0.001

EF- ejection fraction; F - female; GFR - glomerular filtration rate; HbA1c - glycated hemoglobin A1c; Hct - hematocrit; Hbg - hemoglobin; M - male; PASP - pulmonary artery systolic pressure; proBNP - probrain natriuretic peptide

Table 2. A comparison of urocortin 1, adrenomedullin, and proBNP levels using ROC analysis

	Sensitivity (%)	Specificity (%)	AUC	Cut-off	P
ProBNP, pg/mL	100	99.9	0.998	879.5	<0.001
Urocortin 1, pg/mL	98.8	99.9	1.000	260	<0.001
Adrenomedullin, pg/mL	100	99.9	1.000	80	<0.001

AUC - area under the curve

containing tubes. After centrifugation at 2500 x g for 5 min, the plasma and serum were separated for at least 30 minutes. Each sample was divided into four aliquots, and samples were stored at -80°C until biochemical analysis.

Measurement of plasma urocortin 1, adrenomedullin, and proBNP concentrations

Serum UCN1 levels were measured using commercially available ELISA kits (Phoenix Pharmaceuticals, USA). The cross-reactivities documented for the urocortin assay by the manufacturer were 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 adrenomedullin levels were measured using commercially available ELISA kits (Phoenix Pharmaceuticals, USA). For ADM, the limit of quantification was 0.23 nmoL/L; the within-run imprecision (CV) was 1.9%, and the between-run imprecision (CV) was 9.8%. Serum proBNP levels were measured using commercially available kits (Phoenix Pharmaceuticals, USA). Performance in the laboratory included

a limit of quantitation of 5.0 ng/L, within-run imprecision (CV) of 1.5%, and total imprecision (CV) of 3.0%.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 software for Windows (SPSS Inc, Chicago, IL, USA). The normal distribution of data was tested by the 1-sample Kolmogorov-Smirnov test. All statistical comparisons were performed using the unpaired t-test. The unpaired t-test was also validated using the non-parametric Mann-Whitney U test. Chi-square test or Fisher exact test was applied in the comparison of categorical variables. The values were expressed as mean±standard deviation (SD) or the median and interquartile range (IQR, range from the 25th to the 75th percentile). Pearson's correlation was used for numerical data. Spearman's correlation was used for nominal data. To assess the diagnostic accuracy, we performed receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was then estimated. A p value <0.05 was considered to be statistically significant. The results of the intra-assay reproducibility are represented as coefficients of variation.

Results

The general characteristics of the study groups are shown in Table 1. The mean age was 62.5±10.5 in the patient group and 60.1±6.3 in the control group (p=0.075). The gender ratio (F/M) was 38/48 in the patient group and 46/39 in the control group. The age and gender distribution did not differ among groups. The mean left ventricular EF was 31.8±6.8 in the patient group and 60.1±3.4 in the control group (p<0.001). As expected, the EF was lower in the patient group as compared to controls. PASP was significantly higher in the patient group compared to controls (41.8±9.3 mm Hg, 20.1±4.8 mm Hg, respectively; p<0.001).

UCN1, ADM, and proBNP levels were significantly higher in the patient group than in the control group (446.2±147.7, p<0.001; 87.9±4.2, p<0.001; and 7669±5557, p<0.001, respectively). UCN1, ADM, and proBNP levels were compared in terms of their diagnostic ability for heart failure using ROC analysis in Figure 1 and Table 2.

UCN1 was positively correlated with proBNP (r=0.963, p<0.001), ADM (r=0.915, p<0.001), and NYHA (r=0.879, p<0.001); ADM was positively correlated with proBNP (r=0.956, p<0.001) and NYHA (r=0.944, p<0.001); and proBNP was positively correlated with NYHA (r=0.911, p<0.001) in the patient group (Fig. 2-4). EF was negatively correlated with UCN1 (r=-0.427, p<0.001), proBNP (r=-0.471, p<0.001), ADM (r=-0.479, p<0.001), and NYHA (r=-0.342, p=0.001) in the patient group. PASB was positively correlated with UCN1 (r=0.788, p=0.012), proBNP (r=0.932, p<0.001), and ADM (r=0.928, p<0.001) and PASB was negatively correlated with EF (r=-0.957, p<0.001) in the patient group. In the patient, group there were significantly negative correlations between GFR and PASB (r=-0.254, p=0.019). We were unable to demonstrate any correlation between UCN1, ADM, and proBNP levels with age or sex in any subjects.
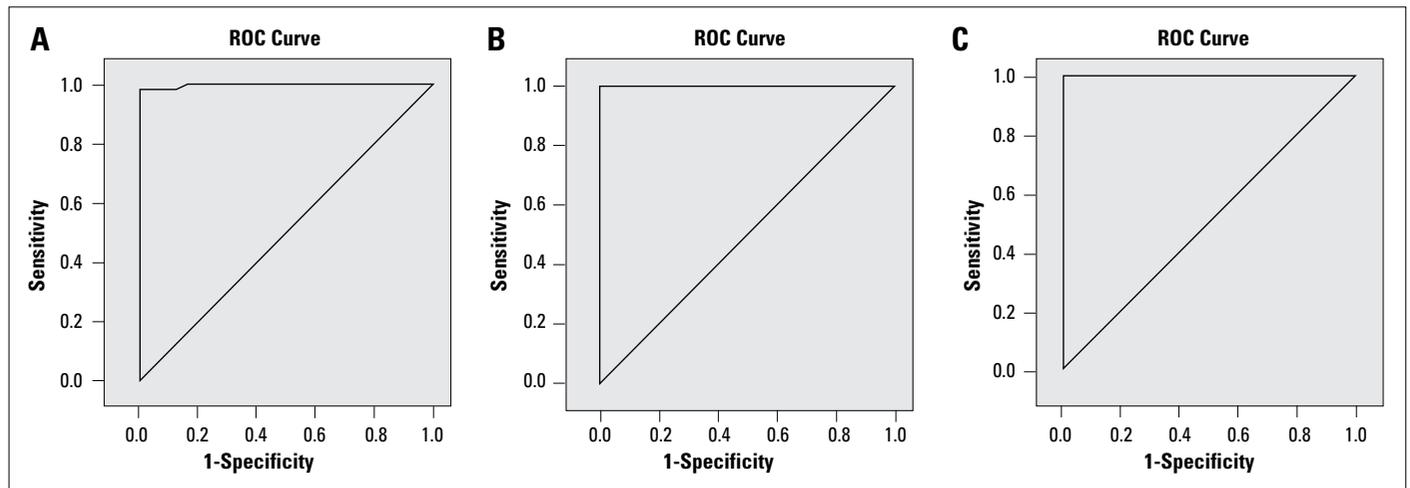
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Figure 1. A-C. A comparison of urocortin 1 (A), adrenomedullin (B), and proBNP (C) levels using ROC analysis
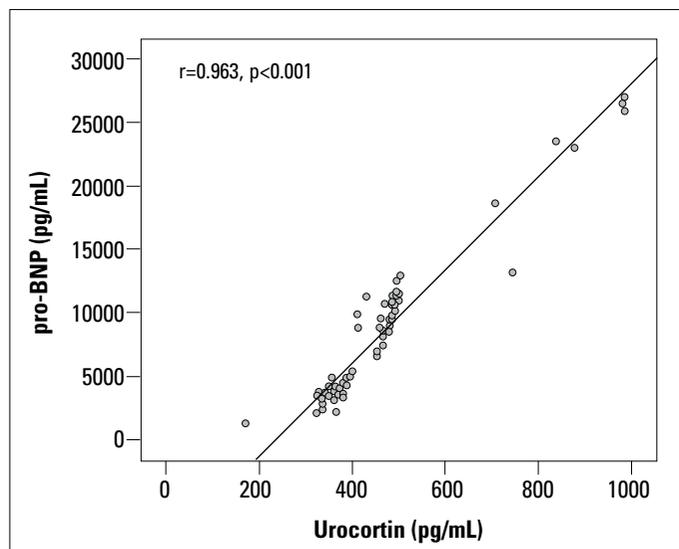

Figure 2. A correlation between proBNP and urocortin 1 levels
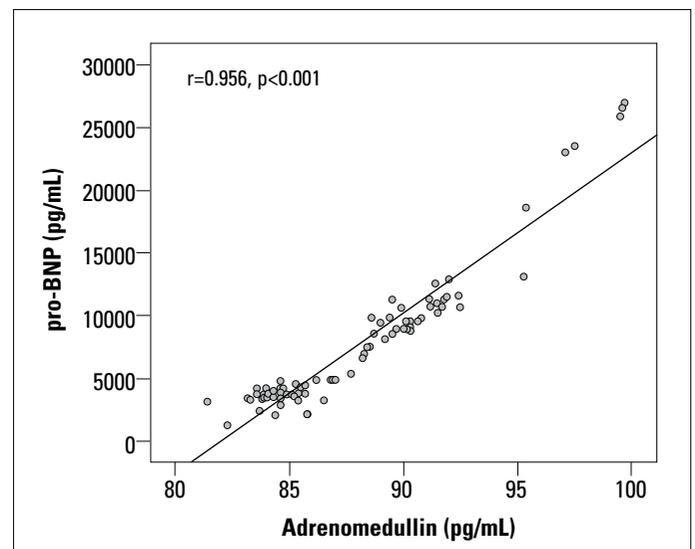
Pearson's correlation

Figure 3. A correlation between proBNP and adrenomedullin levels

Pearson's correlation

Table 3. NYHA functional class in comparing the levels of urocortin 1, ADM, and proBNP in the patient group

	NYHA I-II (n=45)	NYHA III-IV (n=41)	*P*
ProBNP, pg/mL	3785±791	11933±5416	<0.001
Urocortin 1, pg/mL	358±35	542±160	<0.001
Adrenomedullin, pg/mL	84.6±1.2	91.5±3.2	<0.001

Systolic heart failure patients were categorized into two groups according to their NYHA functional class in order to assess and compare the levels of UCN1, ADM, and proBNP with regard to clinical status. While group 1 consisted of stable chronic heart failure patients (NYHA I-II) (n=45), group 2 consisted of decompensated heart failure patients (NYHA III-IV) (n=41). The levels of UCN1, ADM, and proBNP were found to be significantly higher in patients with NYHA III-IV than in patients with NYHA I-II ($p<0.001$, $p<0.001$, and $p<0.001$, respectively) (Table 3).

Discussion

The results of the present study demonstrate that plasma levels of UCN1 and ADM increases in HF patients. UCN1 and ADM levels were positively correlated with pro-BNP and NYHA. 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 increasing 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 (15, 18).

The role of urocortins in the pathophysiology of systolic heart failure has been investigated in previous studies. Some previous studies have demonstrated the plasma levels of urocortin in patients with systolic heart failure (30, 33, 34). Ng et al. (30) reported that urocortin levels were higher in heart failure
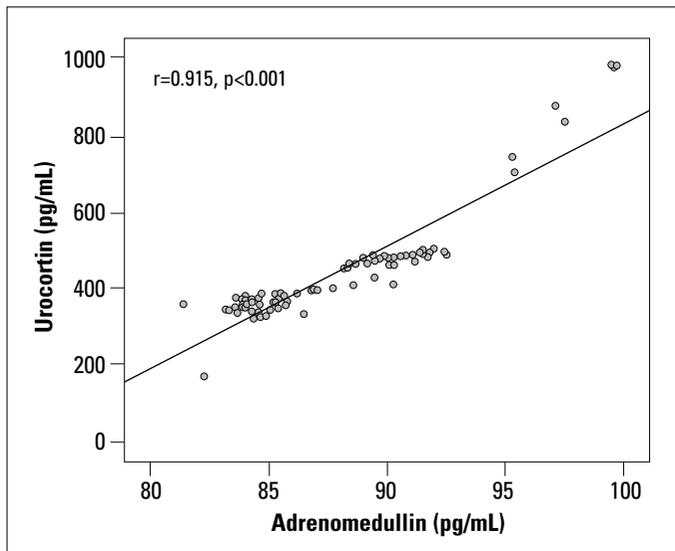
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Figure 4. A correlation between urocortin 1 and adrenomedullin levels
Pearson's correlation

patients; they were lower in the NYHA class III-IV group compared to the NYHA class I-II group. They, just like our study, demonstrated UCN1 levels to increase with increasing NYHA class, from I to IV. They also could not demonstrate any relationships between age, sex, and UCN1 levels, just as in this study.

In various clinical studies, it was demonstrated that plasma UCN1 levels increased with decreasing left ventricular EF (31, 33). We were able to replicate their results. The disparity between the study of Ng et al. (30) and the other investigators, including our results, warrants some attention. Answers may lie within the differing characteristics of the immunoassays used, as suggested by Wright et al. (31). We used a commercially available ELISA kit, like in the study by Gruson et al. (33). In addition to the echocardiographic parameters investigated in the aforementioned studies, we examined the relationship between PASP and UCN1 levels. We managed to demonstrate a positive correlation between PASP values and the levels of UCN1.

The relation between another prognostic factor in heart failure patients, namely, renal function, and UCN1 levels was assessed by Wright et al. (31). They demonstrated an inverse correlation between GFR levels, ADM, and UCN1 (31). In our study, a similar relation between GFR, ADM, and UCN1 was not observed.

ADM is a vasodilator peptide and reduces blood pressure; also, it has natriuretic, antiproliferative, and cell migration-inhibitory properties. It is known that plasma ADM levels increase in pathophysiologic conditions, like arterial hypertension, acute coronary syndrome, heart failure, renal disease, and septic shock (34). In some studies, it was also shown that the plasma ADM levels increase as the severity of symptoms due to NHYA criteria increases in patients with congestive heart failure (35-38). In some previous studies, ADM concentration was shown to be inversely related to the ejection fraction; however, it was found to be directly related to the pulmonary capillary

wedge pressure, ANP, proBNP, and plasma renin activity (35-37). In a study conducted with heart failure patients in Japan, an increase in ADM level was found to be directly related to NYHA, PASP, and pulmonary wedge pressure; however, it was shown to be inversely related to left ventricular ejection fraction (39). In our study, we found that ADM was inversely related to EF; however, it had a direct relationship with proBNP, UCN1, and PASP.

In the BACH study reported in 2010, the diagnostic value of mid-regional pro-atrial natriuretic peptide (MR-proANP) and the prognostic value of mid-regional pro-adrenomedullin (MR-proADM) in patients who presented with acute dyspnea were studied. MR-proANP was shown to have a higher diagnostic value at least as BNP, and MR-proADM was shown to be a strong prognostic marker for 90-day survival (40).

The diagnostic utility of UCN1, ADM, and NT-BNP levels in patients with heart failure has been evaluated previously (31, 33, 41). Ng et al. (30) demonstrated increased sensitivity and specificity with the addition of urocortin measurement to NT-BNP testing in the diagnosis of heart failure. On the other hand, Wright et al. (31) reported a lower diagnostic ability of UCN1, in comparison to NT-BNP [AUC of UCN1 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, UCN1 and ADM were demonstrated to display an effective performance in comparison to proBNP in the diagnosis of heart failure.

In a study of Haehling et al. (42), the levels of mid-regional pro-adrenomedullin (MR-proADM), which is an inactive precursor of ADM, in patients with chronic heart failure were studied. In the 1-year follow-up of 501 chronic heart failure patients, a positive correlation was detected between MR-proADM levels and NYHA class, and increased levels of MR-proADM were found to be related to increased mortality. MR-proADM provides an additional prognostic benefit to NT-proBNP when it is inserted into a basal prognostic model composed of age, EF, creatinine, and NYHA class (42).

In light of the data from Sonma et al. (40) and our study, ADM and urocortin have good diagnostic value at least as proBNP in the diagnosis of acute heart failure; beyond this, they make additional diagnostic contributions when proBNP levels are hard to comment on, and they are better biomarkers than proBNP in cases located in the grey zone.

Study limitations

Since urocortin 1 levels were measured only once during admission, we could not evaluate the changes in urocortin-1 concentrations in the response to treatment due to a lack of serial measurements. Also, the lack of comparison and discussion between urocortin 1 and BNP/NT-proBNP was another limitation of the study. ROC curve analysis could not be done separately according to NYHA class in patients, because the number of patient was limited for a subgroup analysis. These results need to be confirmed in a larger population. The lack of evaluation of the prognostic role of urocortin-1 in systolic heart

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failure due to the cross-sectional design was the last limitation of the present study.

Conclusion

The findings of this study suggest that UCN1 and ADM may be used as diagnostic biomarkers in systolic heart failure, but the incremental value of measuring UCN1 and ADM when considered in patients tested for proBNP levels is questionable. We have demonstrated UCN1 and ADM levels to increase with worsening heart failure, as demonstrated by their positive correlation with NYHA class, proBNP, and PASP and negative correlation with EF. The significance of the inverse relationship between GFR and UCN1 levels needs to be studied further. Also, the role of UCN1 and ADM in the initial diagnosis of diastolic heart failure, along with their possible contribution to the estimation of the prognosis of systolic and diastolic heart failure, needs to be clarified with further studies.

Conflict of interest: None declared.

Peer-review: Partially external peer-reviewed.

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