Relationship of urocortin-2 with systolic and diastolic functions and coronary artery disease: an observational study

Ürocortin-2 ile sistolik, diyastolik fonksiyonlar ve koroner arter hastalığının ilişkisi: Gözlemsel bir çalışma

Ergün Topal, Jülide Yağmur[1], Barış Otlu[2], Halil Ataş[1], Mehmet Cansel[1], Nusret Açıkgöz[1], Necip Ermiş[1]

Clinic of Cardiology, Müjde Hospital, Malatya
[1]Departments of Microbiology and [2]Cardiology, Faculty of Medicine, İnönü University, Malatya-*Turkey*

ABSTRACT

Objective: The urocortin (Ucn) hormones have many important roles in the cardiovascular system. Apart from systolic dysfunction (SD), there is no sufficient data on the relationship between serum Ucn-2 and diastolic dysfunction (DD), or coronary artery disease (CAD). We investigated serum Ucn-2 levels in SD, DD, and CAD.

Methods: In this observational cross-sectional study, study population was enrolled among outpatients who underwent coronary angiography with the pre-diagnosis of CAD. By examining the echocardiography 86 subjects were selected to study after coronary angiography. The subjects distributed over three groups to investigate the relationship between serum Ucn-2 and SD according to their ejection fraction (EF): subjects with moderate to severe SD (Group A, EF=33.6%), subjects with mild to moderate SD (Group B, EF=46.1%), and those without SD (Group C, EF=64.5%). Apart from these groups, the serum Ucn-2 levels were compared between subjects with and without DD (EF≥45%), and also compared between subjects with and without CAD (EF≥55%). Statistical analyses were performed using one-way ANOVA, Kruskal-Wallis, Chi-square, Mann-Whitney U, Spearman correlation and multiple regression analyses tests.

Results: Serum Ucn-2 levels were decreased in Group A and were increased in Group B compared to Group C (9.4±3.4, 12.8±3.6 vs. 10.4±3.9 pg/mL, respectively, p=0.003). Unlike SD; there was no significant difference in serum Ucn-2 levels between subjects with and without DD (11.4±4.1 vs 11.7±3.9 pg/mL, p=0.8) or CAD (10.7±4.7 vs 10.2±3.2 pg/mL, p=0.7).

Conclusion: Ucn-2 is elevated in mild to moderate SD. But, DD (impaired relaxation pattern), or CAD (without myocardial infarction) seems to have no effect on Ucn-2 hormone levels. *(Anadolu Kardiyol Derg 2012; 12: 115-20)*

Key words: Urocortin 2, left ventricular systolic and diastolic dysfunction, coronary artery disease, regression analysis

ÖZET

Amaç: Urocortin (Ucn) hormonları kardiyovasküler sistemde önemli rol oynamaktadır. Sistolik işlev bozukluğu (SD) dışında, diyastolik işlev bozukluğu (DD) veya koroner arter hastalığının (KAH) serum Ucn-2 ile ilişkisine dair yeterli veri bulunmamaktadır. Bu çalışmamızda SD, DD ve KAH'da serum Ucn-2 düzeyini araştırdık.

Yöntemler: Bir gözlemsel enine-kesitli olan bu çalışmanın popülasyonu KAH ön tanısı ile koroner anjiyografi işlemine alınan bireyler arasından belirlendi. Koroner anjiyografi sonrası ekokardiyografi yapılarak 86 kişi seçildi. Ucn-2 ile SD arasındaki ilişkiyi araştırmak için ejeksiyon fraksiyonu (EF) farklı üç grup oluşturuldu: orta-ileri düzey SD olanlar (Grup A, EF=%33.6), hafif-orta SD olanlar (Grup B, EF=%46.1) ve SD olmayanlar (Grup C, EF= %64.5). Ayrıca, DD sahip olan ve olmayanlar (EF≥ %45) arasında ve KAH'ı olan ve olmayanlar (EF≥ %55) arasında da Ucn-2 düzeyi karşılaştırıldı. İstatistiksel analizde tek yönlü ANOVA, Kruskal-Wallis, Ki-kare, Mann-Whitney U, Spearman korelasyon ve çoklu regresyon testleri kullanıldı.

Bulgular: Grup C'ye göre, Ucn-2 düzeyinin Grup A'da azaldığı ve Grup B'de arttığı saptandı (Grup A, B ve C'de sırasıyla Ucn-2; 9.4±3.4, 12.8±3.6 ve 10.4±3.9 pg/mL, p=0.003). SD'den farklı olarak; Ucn-2 düzeyi bakımından, DD olan ve olmayanlar arasında (11.4±4.1 ve 11.7±3.9 pg/mL, p=0.8) veya KAH olan ve olmayanlar arasında (10.7±4.7 ve 10.2±3.2 pg/mL, p=0.7) anlamlı bir fark saptanmadı.

Sonuç: Serum Ucn-2 düzeyi hafif-orta sistolik disfonksiyonda yükselmektedir. Ancak, DD (azalmış gevşeme bozukluğu) veya KAH'ın (miyokart enfarktüsü olmadan) serum Ucn-2 düzeyini etkilemediği görülmektedir. *(Anadolu Kardiyol Derg 2012; 12: 115-20)*

Anahtar kelimeler: Urocortin-2, sol ventrikül sistolik ve diyastolik işlev bozukluğu, koroner arter hastalığı, regresyon analizi

Address for Correspondence/Yazışma Adresi: Dr. Ergün Topal, Müjde Hastanesi, Kardiyoloji Kliniği, Hastane Cad. No: 16, Malatya-*Türkiye*
Phone: +90 422 444 23 44 Fax: +90 422 241 07 28 E-mail: ergun2010@hotmail.com

Accepted Date/Kabul Tarihi: 18.10.2011 **Available Online Date/Çevrimiçi Yayın Tarihi:** 26.01.2012

doi:10.5152/akd.2012.036

Introduction

In recent studies, novel corticotropin releasing factor (CRF)-related peptides, named Ucn-1, Ucn-2, and Ucn-3 have been identified (1-3). The actions of these peptides are mediated by binding to two G-coupled receptors; CRF receptor type 1 and 2 (CRF-R_1, CRF-R_2) (1-4). CRF-R_1 is found predominantly in the pituitary and brain regions, whereas the CRF-R_2 is more localized in the heart chambers and peripheral vascular system (1-6). Although Ucn-1 binds to both receptors, Ucn-2 and Ucn-3 show more affinity to CRF_2 receptor (2, 3). Kimura et al. (7) reported that urocortins and CRF_2 receptor were detected in all chambers of human hearts, especially in the left ventricle.

The available evidence from animal models and human clinical studies indicate that urocortins have many important pathophysiological and regulatory roles in the cardiovascular system. These effects of urocortins can be summarized as follows; a dose-dependent increase in heart rate, cardiac output, coronary blood flow (8), coronary vasodilatation and positive inotropic effect (9), protection against ischemic and reperfusion injury in ventricular myocytes, a diminution in free radical damage following myocardial infarction (10, 11), stimulation of cardiac natriuretic peptide secretion, decrease in left atrial pressure and peripheral vascular resistance (12), decrease in blood pressure, reduction of serum catecholamine levels in hyperadrenergic hypertension (13).

It has been known that heart failure (HF) is a complex syndrome, characterized by the progressive activation of a series of neuroendocrine hormones; such as norepinephrine, angiotensin II, aldosterone, and endothelin. Acting locally and systemically these hormones cause unfavorable effects in HF process. Endothelin and natriuretic peptides are predictors for prognosis and left ventricle dysfunction in HF (14). In a blood sample practically measurement of such determinants may contribute to the improvement of quick diagnosis of HF and could allow to detect the staging of HF. The published results show that Ucn is a diagnostic marker and a potentially attractive therapeutic target for HF (13, 15-17). Relatively few studies (18-20) have been performed related to the role of Ucn hormone in humans HF, and there are no sufficiently investigations regarding relation of serum Ucn levels with diastolic dysfunction (DD) or CAD.

The aim of this study was to investigate serum Ucn-2 levels in subjects with systolic dysfunction (SD), DD and CAD.

Methods

Study design and sample size

This observational cross-sectional study included 86 subjects (62±10 years, 36 women). Demographic characteristics and known to be traditional risk factors for CAD were inquired (Table 1). Different study groups were composed to investigate serum Ucn-2 levels in 86 subjects. The appropriate sample size for the study was assessed by power analysis, with 27 patients in each group, a power of 80% would be achieved (α=0.05, power=80%, n=27 in each group).

Study population

The study subjects enrolled to study between April and June 2010 at the İnönü University. The study population were selected among hemodynamically stable outpatients who consecutively underwent coronary angiography with the pre-diagnosis of CAD. Study population had anginal symptoms or ischemic findings in laboratory tests. They had SD, DD or normal ventricular functions and coronary angiography was performed without considering left ventricle functions. The patients with SD or DD had NYHA 1, 2 functional class and many patients with ejection fraction (EF) ≤40% were under HF treatment. Angiograms were examined by an experienced interventional cardiologist, who was blinded to indication for angiography. After coronary angiography, by examining the transthoracic echocardiography and eliminating according to exclusion criteria, 86 subjects were selected finally. To investigate between serum Ucn-2 levels and SD, DD and CAD different study groups were composed and three separate comparison were carried out: (1) between subjects with SD (Group A; subjects with moderate to severe SD, EF ≤40%, n=27 / Group B; subjects with mild to moderate SD, EF=40-55%, n=29) and without SD (Group C; EF ≥55%, n=30), (2) between subjects with DD (EF ≥45%, n=34) and without DD (EF ≥45%, n=14), and (3) between subjects with CAD (EF ≥55%, n=14) and without CAD (EF ≥55%, n=16).

Exclusion criteria were as follows; (1) patients with NYHA functional class 3 or 4, (2) concomitant liver, thyroid or kidney diseases, (3) acute coronary syndrome status (patients were excluded which requiring emergency angiographic evaluation or primary percutaneous intervention due to acute coronary syndrome), (4) severe valvular disease, (5) severe chronic obstructive pulmonary disease.

All subjects gave written informed consent and the study was approved by the Local Ethics Committee.

Study variables

The clinical variables including age, gender, body mass index, and major risk factors for CAD and laboratory (echocardiographic) variables are summarized in Table 1.

The outcome variable of study was serum Ucn-2. Predictor variables were: SD-defined as above: mild-moderate, moderate-severe SD and absence of SD; DD-defined as presence or absence of DD (see below definitions) and presence or absence of CAD. The patients with ≥50% occlusion in at least one coronary artery on angiogram were accepted as those with CAD.

Echocardiography

The EF values were determined using transthoracic echocardiographic measurement (ATL HDI-5000 Bothell, Washington, USA), after coronary angiography, during bed rest, within 6 hours. The SD grading on the echocardiogram was calculated a

Table 1. Clinical characteristics of the groups

Variables	Group A (n=27)	Group B (n=29)	Group C (n=30)	*χ^2 or *F	*p
Age, year	69 (52-83)[a,b]	64 (30-80)	58 (35-79)	8.2	0.001
Gender, female, n (%)	11 (40)	14 (48)	11 (36)	0.8	0.7
Body mass index, kg/m^2	25 (21-28)	27 (22-31)	27 (18-33)	3.1	0.049
Hypertension, n (%)	14 (51)	18 (62)	18 (60)	0.6	0.5
Diabetes mellitus, n (%)	9 (33)	12 (41)	9 (30)	0.8	0.7
Hyperlipidemia	11 (40)	9 (31)	16 (53)	3.0	0.3
Smoking, n (%)	15 (55)	19 (65)	11 (36)	5.0	0.5
Glucose, mg/dL	118 (74-286)	102 (65-307)	106 (79-311)	1.2	0.5
LDL cholesterol, mg/dL	104 (23-189)	100 (54-169)	117 (63-209)	0.5	0.6
Triglyceride, mg/dL	148 (64-339)	152 (56-360)	171 (42-397)	0.2	0.8
Ucn-2, pg/mL	8.9 (4.2-16.6)[a]	12.7 (4.9-18.6)[c]	11.0 (4.1-17.7)	6.2	0.003
CAD	21(77)	23(79)	14(46)	9.0	0.01
Echocardiographic variables					
LVEF, %	34 (25-40)[a,b]	45 (42-54)[c]	64 (55-73)	75.5	<0.001
LVEDD, mm	56 (46-69)[a,b]	48 (42-65)[c]	45 (38-57)	37.5	<0.001
LVESD, mm	42 (36-49)[a,b]	35 (30-47)[c]	29 (26-38)	58.7	<0.001
E-wave velocity, cm/s	59 (20-76)[b]	55 (20-90)	57 (32-89)	4.9	0.01
A-wave velocity, cm/s	59 (20-76)[a]	58 (25-76)[c]	69 (30-120)	8.3	<0.001
E/A ratio	0.7 (0.3-2.3)	0.8 (0.4-2.5)	0.7 (0.4-1.7)	1.5	0.4
Em velocity, cm/s	7.0 (3.7-9.8)[b]	6.5 (3.8-11.2)[c]	8.6 (4.3-17.8)	12.6	0.002
E/Em ratio	6.9 (3.3-12.6)	7.4 (4.0-12.6)	6.6 (3.1-14.3)	0.9	0.6
Deceleration time, ms	225 (70-330)	195 (90-320)	200 (100-315)	1.2	0.2
IVRT, ms	105 (50-150)	110 (75-145)[c]	92 (55-140)	3.7	0.02

Data are presented as median (min-max) and number (percentage) values
*one-way ANOVA, Kruskal-Wallis, or Chi-square tests
post hoc paired comparisons of Tukey or Mann-Whitney U test: [a]between Group A and B, [b]between Group A and C, [c]between Group B and C; p<0.05
A - transmitral flow velocity during late filling, CAD - coronary artery disease, E - transmitral flow velocity during early filling, Em - mitral annular flow velocity during early filling, IVRT - isovolumetric relaxation time, LDL - low-density lipoprotein, LVEDD - left ventricular end-diastolic diameter, LVEF - left ventricular ejection fraction, LVESD - left ventricular end-systolic diameter, Ucn-2 - urocortin-2

quantitative, apical biplane modified Simpson's method and EF predictive values of Group A, B and C were classified in accordance with recommendations of American Society of Echocardiography (ASE) (21). The diastolic dysfunction parameters; ratio of transmitral flow velocities during early and late filling (E/A ratio), ratio of transmitral flow velocity to mitral annular velocity during early filling (E/Em ratio), deceleration time (DT), and isovolumetric relaxation time (IRVT) were recorded by Doppler echocardiography. We determined the presence of diastolic dysfunction and grading according to guidelines from the ASE (22). Diastolic dysfunction was assessed using transmitral Doppler inflow velocity patterns and Doppler tissue imaging (average of septal and lateral mitral annulus Doppler signals). Normal diastolic pattern was defined; E/A=0.75-1.5, DT=150-220 ms, IVRT<100 ms, E/Em ≤8. Grade 1 diastolic dysfunction was defined as impaired relaxation; E/A <0.8, DT>200 ms, IVRT≥100 ms, E/Em ≤8. Grade 2 DD was defined as a pseudonormal filling pattern; E/A=0.8-1.5, DT=160-200 ms, IVRT=60-100, E/Em=9-12. Grade 3 diastolic dysfunction was defined as a restrictive filling pattern; E/A ≥2, DT<160ms, IVRT≤60, E/Em>13 (22, 23).

Ucn-2 assay

Venous blood samples for Ucn-2 assays were taken in serum separator tubes from the resting subjects after echocardiographic examination. All blood samples were centrifuged at 3000 rpm for 10 min. The sera were separated and stored as two aliquots at -80°C in the polypropylene tubes, until the assay of Ucn 2. Quantitative analysis of Ucn-2 in serum samples of subjects was detected by using Human Urocortin II ELISA Kit (detection range: 6.25-400 pg/mL) which was maintained from Cusabio Biotech Co. Ltd, China (Lot No:C04051522). The principle of that assay depends on competitive ELISA method. The Ucn level was

measured according to the manufacturerıs protocol. Optic density values were analyzed according to the values of standards.

Statistical analysis

Data were analyzed on SPSS version 15.0 for Windows statistical package (SPSS, Chicago, IL, USA). The parameters were evaluated for normality and the distribution and homogeneity of variances were verified. The parameters satisfying these conditions were examined with one-way ANOVA, otherwise Kruskal-Wallis test was performed to compare the difference between three groups. Post-hoc Tukey test or Mann-Whitney U test was used to determine the differences of paired groups analysis in Group A, B and C. The differences in proportions among the three groups were analyzed using Chi-square test. Multiple regression analysis was used to evaluate the effects of all independent factors that potentially affect the serum Ucn 2.

Results

Demographic and clinical characteristics of the population and Ucn-2

Clinically and hemodynamically stable (before and after coronary angiography) subjects were selected. Demographic parameters were not different among groups and more than 50% of the subjects had hypertension and nearly half had other coronary risk factors (Table 1). We did not find any significant relationship between serum Ucn-2 levels and other parameters (age, gender, coronary artery risk factors, CAD and left ventricular dimensions) among the groups; there was no or weak relationship, Spearman's rank correlation test, r=close to zero. Although we observed differences in age, BMI and CAD parameters between groups (Table 1), no relation detected in a multiple regression analysis after adjustment for age (p=0.3), BMI (p=0.5), and CAD (p=0.8) with Ucn 2. Because our study not included the patients with NYHA functional class 3 or 4 or acute dyspneic attack, we could not investigate the relationship between Ucn-2 levels and NYHA functional class.

SD, DD and Ucn-2 (Table 1).

Comparison of Ucn-2 levels in SD groups demonstrated a decrease in Group A, an increase in Group B compared to normal EF Group (Group C) and serum Ucn-2 levels were 9.4, 12.8, 10.4 pg/mL, respectively (p=0.003) (Fig. 1).

We also compared the serum Ucn-2 levels between subjects with and without DD. The patients with DD were in Group B and C (EF ≥45%, mean EF=57±9, n=34). Twenty-five subjects had Grade 1 (73%) and, 9 subjects had Grade 2 DD (none had Grade 3). Those without diastolic abnormalities were 14 patients (EF ≥45%, mean EF=61±8%). No significant association or correlation were observed in Ucn-2 levels, compared between subjects with DD and without DD (11.4±4.1 vs 11.7±3.9 pg/mL; p=0.8, r=-0.04), or compared subjects with Grade 1 DD and Grade 2 DD (11.5±4.1 vs 11.1±4.6; p=0.9).

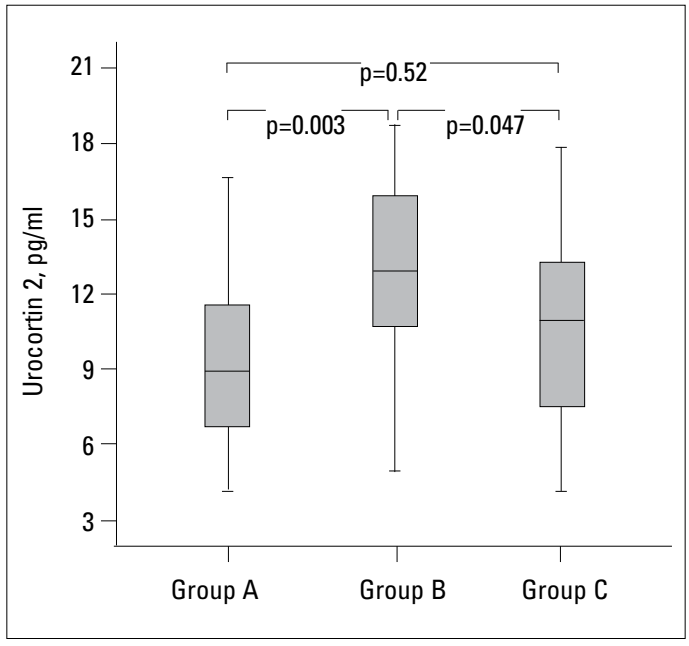

Figure 1. The range of serum urocortin-2 levels of the groups
The box plots represent the median, first and third quartiles, minimum and maximum data values
Kruskal-Wallis test
The comparison between the groups; p=0.003 (Group A and B), p=0.52 (Group A and C) and p=0.047 (Group B and C)

CAD and Ucn-2

Furthermore, the individuals of Group C (n=30, mean EF:64±4%) were selected from study subjects to assess the relationship between the serum Ucn-2 levels and CAD. To eliminate the impact of left ventricular systolic dysfunction on serum Ucn-2 levels, subjects with >55% EF were included to study and there were 14 patients with CAD (46%) versus 16 without CAD. These patients had predominantly status as Canadian angina class 3 or less. No statistical differences in serum Ucn-2 were detected between the patient with CAD group and those without CAD (Ucn-2= 10.7±4.7 vs 10.2±3.2 pg/mL; p=0.7). A similar result was also seen when taken as a threshold EF value ≥45% (n=23 vs. 19; Ucn-2=11.1±4.5 vs 10.9±3.5 pg/mL; p=0.8).

Discussion

In our study, we detected elevated serum Ucn-2 in mild to moderate systolic dysfunction (Fig. 1). But, DD (impaired relaxation pattern), or CAD (without myocardial infarction) did not affect the serum Ucn-2 hormone levels.

Over the recent few decades there have been striking advances in understanding of the pathogenesis of HF at molecular basis. Neurohormonal activation rise early after the onset of the deterioration of hemodynamic conditions. B-type natriuretic peptides are well-known peptide hormones, have a considerable role in the diagnosis of HF. Several novel cardiac neurohormonal biomarkers (chromogranin A, apelin, galectin-3, adrenomedullin, ST2, adiponectin, etc.) have been identified in HF (24-26), they

are still under investigation because of bringing potential diagnostic and therapeutic notion (role) in HF. The Ucn hormone is a group of peptides acting on specific G-coupled CRF receptors. Ucn-2 shows a greater affinity to CRF-R_2 and it is found predominantly in the heart chambers and peripheral vascular system (1-3). The available evidence from several animal models and human clinical studies is considered that the urocortins have many pathophysiological and regulatory roles in the cardiovascular system (8-13). Also Ucn-2 infusion has improved cardiac output and EF and reduced systemic vascular resistance and a cardiac work in human cases of HF (15).

Relatively few human studies are available in patients with HF on Ucn hormone. The researchers performed the experimental or clinical studies in relation to Ucn family (Ucn, Ucn-1, Ucn-2, and Ucn-3) (8-17). Ng et al. (18) are the first researchers to explore the elevated levels of serum Ucn in human systolic HF, especially in early stages of HF, when compared with healthy controls. They suggested that Ucn system has an up-regulatory role, might be cardioprotective in the early stages of HF. On the other hand, Wright et al. (19) reported elevated plasma Ucn-1 hormone, and Gruson et al. (20) also reported increased plasma Ucn hormone levels in HF in proportion with the degree of cardiac dysfunction according to NYHA functional class I to IV. Unlike these studies, our study excluded the patients with NYHA 3 and 4, and clinically decompensated HF cases. We investigated levels of serum Ucn-2 hormone in outpatients with moderate to severe depressed left ventricular function (Group A; mean EF=33, 25-39%), mild to moderate depressed systolic function (Group B; mean EF=40, 40-54%), and normal systolic function (Group C; mean EF=64, 55-70%). Elevated serum Ucn-2 levels found in Group B (Fig. 1). Similar to Ng et al. (21)'s study, we also observed that Ucn-2 levels were not elevated in severe left ventricular dysfunction (differently they tested serum Ucn hormone, instead of Ucn-2). Our results indicated that levels of circulating Ucn-2 changed in left ventricular dysfunction, and there was no or a weak linear correlation between Ucn-2 levels and age or other cardiovascular risk factors using multiple regression analysis. The mechanism of stimulating the secretion of Ucn-2 hormone in early HF is not clear. The previous studies indicated that an activated serum Ucn hormones were related to anti-inflammatory response (reducing the interleukin and tumor necrotizing factor secretion), in exaggerated hyperadrenergic state, or as a cardioprotective role of Ucn (Ucn-1, Ucn-2 isoforms and Ucn) in HF process (12, 13, 27, 28). The reason for the lack of the serum Ucn-2 response in the presence of moderate to severe left ventricular dysfunction (Group A) may be due to withdrawal of anti-inflammatory and cardioprotective response in HF process.

In the light of current studies, it is difficult to say which Ucn hormone or isoform is predictor for systolic HF or threshold level of EF. Regarding the specificity of the assay; unlike Ucn-1, Ucn-2 is highly selective for the CRF_2 receptor and does not show affinity for the CRF binding protein (2), and we used commercially available Ucn-2 ELISA Kit (Cusabio Biotech Co., Ltd, China) which allows for the in vitro quantitative determination of human Ucn-2 concentrations in serum, plasma and other biological fluids. Kit manufacturer declared that this assay recognizes recombinant and natural human Ucn-2, and no significant cross-reactivity or interference was observed. Additionally we measured Ucn-2 level in serum, not in the tissue samples. Further studies will clarify the role of urocortins in the pathophysiology, diagnosis, and therapeutics of evolving of HF. Ucn-2 may not be as powerful as the natriuretic peptides in the diagnosis of HF for the present, but therapeutic features of Ucn hormone (Ucn-1, Ucn-2 isoforms) (13, 15-17) are seems to distinctive from the natriuretic peptides.

Apart from the patients with systolic HF, we also measured Ucn-2 levels between subjects with and without DD (EF ≥45%) and between subjects with and without CAD (EF ≥55%). There was no relationship between serum Ucn-2 levels and DD, or CAD. The patients with DD predominantly (73%) had Grade 1 DD (slowed relaxation pattern). Worsening in DD or a prominent increase in left atrial pressure probably may change serum Ucn-2 levels. Tang et al. (29) demonstrated that higher levels of plasma levels of Ucn-1 and endothelin-1 were associated with worse left ventricle diastolic performance and poorer long-term clinical outcomes in patients with chronic systolic HF. Differently, they tested Ucn-1 hormone, selected patients had NYHA 1-4 class and severe left ventricular dysfunction (EF≤ 40, mean EF=25±6%, diastolic Grade 3=36%).

In context of CAD, the studies introduced that Ucn-2 induces the vasorelaxation of coronary arteries independent from endothelial cell activation (9), plasma Ucn is elevated in acute myocardial infarction, and Ucn-1, Ucn-2 may play a protective in ischemia-reperfusion injury (10, 11, 30). Whereas, we could not demonstrate a change in Ucn-2 levels in our patients with CAD.

Study limitations

Limitations of our study as follows; (1) the study did not include patients with functional Class 3, 4 heart failure, (2) a difference in the heart failure treatment regimes for the three groups may have an influence on results. In generally, study subject's therapy was varied personally, and it could not take statistically sufficient data from three groups about therapy, (3) we could not make a comparison of the Ucn isoforms (Ucn 1, 2, and 3) to detect whether there is a difference between isoforms.

Conclusion

In conclusion, our results suggest that serum Ucn-2 concentrations increase in patients with mild to moderate left ventricular systolic dysfunction. On the other hand, CAD without myocardial infarction, or DD (impaired relaxation pattern) seems to have no effect on serum Ucn-2 hormone levels. In the varied spectrum of these diseases, further investigations will be enlightening.

Conflict of interest: None declared.

Authorship contributions: Concept - E.T., J.Y., Design - E.T., J.Y., B.O., H.A.; Supervision - J.Y., B.O., H.A.; Resources - E.T., J.Y., N.E., N.A., M.C.; Material - E.T., B.O.; Data collection&/or Processing: E.T., J.Y., H.A.; Analysis &/or Interpretation - E.T., J.Y., B.O.; Literature Search - E.T.; Writing - E.T.; Critical review - B.O., N.E., N.A., M.C.

References

1. Vaughan J, Donaldson C, Bittencourt J, Perrin MH, Lewis K, Sutton S, et al. Urocortin, a mammalian neuropeptide related to fish urotensin I and to corticotropin-releasing factor. Nature 1995: 378; 287-92. [CrossRef]
2. Reyes TM, Lewis K, Perrin MH, Kunitake KS, Vaughan J, Arias CA, et al. Urocortin II: a member of the corticotropin-releasing factor (CRF) neuropeptide family that is selectively bound by type 2 CRF receptors. Proc Natl Acad Sci U S A 2001; 27: 2843-8. [CrossRef]
3. Lewis K, Li C, Perrin MH, Blount A, Kunitake K, Donaldson C, et al. Identification of urocortin III, an additional member of the corticotropin-releasing factor (CRF) family with high affinity for the CRF2 receptor. Proc Natl Acad Sci U S A 2001; 19: 7570-5. [CrossRef]
4. Dautzenberg FM, Hauger RL. The CRF peptide family and their receptors: yet more partners discovered. Trends Pharmacol Sci 2002; 23: 71-7. [CrossRef]
5. Iino K, Sasano H, Oki Y, Andoh N, Shin RW, Kitamoto T, et al. Urocortin expression in the human central nervous system. Clin Endocrinol 1999; 50: 107-14. [CrossRef]
6. Baigent SM, Lowry PJ. mRNA expression profiles for corticotrophin-releasing factor (CRF), urocortin, CRF receptors and CRF-binding protein in peripheral rat tissues. J Mol Endocrinol 2000; 25: 43-52. [CrossRef]
7. Kimura Y, Takahashi K, Totsune K, Muramatsu Y, Kaneko C, Darnel AD, et al. Expression of urocortin and corticotropin-releasing factor receptor subtypes in the human heart. J Clin Endocrinol Metab 2002; 87: 340-6. [CrossRef]
8. Parkes DG, Vaughan J, Rivier J, Vale W, May CN. Cardiac inotropic actions of urocortin in conscious sheep. Am J Physiol 1997; 272: H2115-22.
9. Terui K, Higashiyama A, Horiba N, Furukawa KI, Motomura S, Suda T. Coronary vasodilation and positive inotropism by urocortin in the isolated rat heart. J Endocrinol 2001; 169: 177-83. [CrossRef]
10. Brar BK, Jonassen AK, Stephanou A, Santilli G, Railson J, Knight RA, et al. Urocortin protects against ischemic and reperfusion injury via a MAPK-dependent pathway. J Biol Chem 2000; 275: 8508-14. [CrossRef]
11. Barry SP, Lawrence KM, McCormick J, Soond SM, Hubank M, Eaton S, et al. New targets of urocortin-mediated cardioprotection. J Mol Endocrinol 2010; 45: 69-85. [CrossRef]
12. Rademaker MT, Charles CJ, Espiner EA, Frampton CM, Lainchbury JG, Richards AM. Four-day urocortin-I administration has sustained beneficial haemodynamic, hormonal and renal effects in experimental heart failure. Eur Heart J 2005; 26: 2055-62. [CrossRef]
13. Gu Y, Zhang K, Biswas N, Friese RS, Lin DH, Mahata SK, et al. Urocortin 2 lowers blood pressure and reduces plasma catecholamine levels in mice with hyperadrenergic activity. Endocrinology 2010; 151: 4820-9. [CrossRef]
14. Van Beneden R, Gurné O, Selvais PL, Ahn SA, Robert AR, Ketelslegers JM, et al. Superiority of big endothelin-1 and endothelin-1 over natriuretic peptides in predicting survival in severe congestive heart failure: a 7-year follow-up study. J Card Fail 2004; 10: 490-5. [CrossRef]
15. Davis ME, Pemberton CJ, Yandle TG, Fisher SF, Lainchbury JG, Frampton CM, et al. Urocortin 2 infusion in human heart failure. Eur Heart J 2007; 28: 2589-97. [CrossRef]
16. Dieterle T, Meili-Butz S, Bühler K, Morandi C, John D, Buser PT, et al. Immediate and sustained blood pressure lowering by urocortin 2: a novel approach to antihypertensive therapy? Hypertension 2009; 53: 739-44. [CrossRef]
17. Rademaker MT, Charles CJ, Nicholls G, Richards M. Urocortin 2 sustains haemodynamic and renal function during introduction of beta-blockade in experimental heart failure. J Hypertens 2011; 29: 1787-95. [CrossRef]
18. Ng LL, Loke IW, O'Brien RJ, Squire IB, Davies JE. Plasma urocortin in human systolic heart failure. Clin Sci (Lond) 2004; 106: 383-8. [CrossRef]
19. Wright SP, Doughty RN, Frampton CM, Gamble GD, Yandle TG, Richards AM. Plasma urocortin 1 in human heart failure. Circ Heart Fail 2009; 2: 465-71. [CrossRef]
20. Gruson D, Ahn SA, Ketelslegers JM, Rousseau MF. Circulating levels of stress associated peptide Urocortin in heart failure patients. Peptides 2010; 31: 354-6. [CrossRef]
21. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005; 18: 1440-63. [CrossRef]
22. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. J Am Soc Echocardiogr 2009; 22: 107-33. [CrossRef]
23. Khouri SJ, Maly GT, Suh DD, Walsh TE. A practical approach to the echocardiographic evaluation of diastolic function. J Am Soc Echocardiogr 2004; 17: 290-7. [CrossRef]
24. Braunwald E. Biomarkers in heart failure. N Engl J Med 2008; 358: 2148-59. [CrossRef]
25. van Kimmenade RR, Januzzi JL Jr, Ellinor PT, Sharma UC, Bakker JA, Low AF, et al. Utility of amino-terminal pro-brain natriuretic peptide, galectin-3, and apelin for the evaluation of patients with acute heart failure. J Am Coll Cardiol 2006; 48: 1217-24. [CrossRef]
26. Daniels LB, Clopton P, Iqbal N, Tran K, Maisel AS. Association of ST2 levels with cardiac structure and function and mortality in outpatients. Am Heart J 2010; 160: 721-8. [CrossRef]
27. Agnello D, Bertini R, Sacco S, Meazza C, Villa P, Ghezzi P. Corticosteroid-independent inhibition of tumor necrosis factor production by the neuropeptide urocortin. Am J Physiol 1998; 275: E757-62.
28. Yuan Z, McCauley R, Chen-Scarabelli C, Abounit K, Stephanou A, Barry SP, et al. Activation of Src protein tyrosine kinase plays an essential role in urocortin-mediated cardioprotection. Mol Cell Endocrinol 2010; 325: 1-7. [CrossRef]
29. Tang WH, Shrestha K, Martin MG, Borowski AG, Jasper S, Yandle TG, et al. Clinical significance of endogenous vasoactive neurohormones in chronic systolic heart failure. J Card Fail 2010; 16: 635-40. [CrossRef]
30. Phrommintikul A, Sivasinprasasn S, Lailerd N, Chattipakorn S, Kuanprasert S, Chattipakorn N. Plasma urocortin in acute myocardial infarction patients. Eur J Clin Invest 2010; 40: 874-82. [CrossRef]