Further evidence to support a role for urocortin 2 in heart failure

Kalp yetersizliğinde urocortin-2'nin rolünü destekleyen daha fazla kanıt

The urocortin (UCN) group comprises 3 structurally-related peptides which are included within the corticotropin-releasing factor family (1-3). Specific receptors for UCN2 and 3 are expressed throughout the vasculature and myocardium (4), suggesting a role for these peptides in maintaining cardiovascular homeostasis. More recently, the UCNs are receiving increasing clinical interest due to a growing body of data from human, animal and *in vitro* studies, which highlight the therapeutic potential of these peptides. In particular, reports of improved cardiac output in heart failure patients treated with UCN2 and observed correlations of circulating UCN1 with cardiovascular disease severity confirm that the urocortins may be novel therapeutic, diagnostic and prognostic targets [discussed in detail in ref. 5].

In the current issue of the *Anatolian Journal of Cardiology,* Topal et al. (6) investigate the relationship between serum UCN2 and a range of cardiovascular pathologies including systolic dysfunction, diastolic dysfunction and coronary artery disease. To date, circulating UCN2 has not been widely investigated in heart disease. The study is conducted in a population of hemodynamically stable patients undergoing coronary angiography at Inönü University (n=86). Trans-thoracic echocardiograms were used to subdivide this population according to left ventricular ejection fraction (EF), giving rise to 3 groups of patients with varying degrees of systolic dysfunction. The most significant finding of this study is the observation that serum UCN2 is significantly elevated in patients with moderate systolic dysfunction (EF 40-55%), compared to individuals with severe- (EF ≤40%), or no- (EF≥55%) systolic dysfunction. A trend towards decreased serum UCN2 is reported in cases of severe systolic dysfunction (EF ≤40%) compared to patients with normal ejection fraction, although statistical significance could not be demonstrated in this case (p=0.52). Secondary comparisons revealed no association between serum UCN2, diastolic dysfunction or coronary artery disease in the absence of myocardial infarction.

The mechanisms underpinning the observed relationship between serum UCN2 and systolic dysfunction remains unclear. The authors hypothesize that increased secretion of UCN2 in early stage heart disease may be a mechanism by which the body attempts to minimize pathological processes. They further suggest that reduced serum UCN2 in patients with severe systolic dysfunction may be indicative of increased myocardial inflammation in advanced heart failure. Evidence from other studies demonstrates that serum UCN1 increases in association with advancing heart disease (5, 7, 8), although it is possible that different UCN species act differently during heart failure. Further investigation is warranted to test this hypothesis.

Although interesting, care must be taken when interpreting these results. This study was conducted in a relatively small patient population (total n=86), which was further subdivided to conduct the various comparisons. Although the power calculations generated by the authors suggest that the group sizes employed were sufficient to achieve 80% power (α=0.05), larger-scale studies with higher statistical sensitivity are warranted to validate findings presented here. In addition, the authors highlight the fact that patients with NYHA functional class 3 or 4 heart failure were ineligible for inclusion from the study, thus the association of UCN2 in advanced heart failure could not be addressed. Importantly, this study is limited to the investigation of UCN2, thus serum profiles of other UCN peptides could not be assessed in this population.

In conclusion, the observation of increased UCN2 in patients with moderate to severe left ventricular systolic dysfunction is encouraging, although the biomarker value of this peptide remains in question. Blood-borne markers for chronic disease are an attractive prospect due to the ability to rapidly assess a broad spectrum of patients in a non-invasive manner, however in complex pathologies such as heart failure it seems unlikely that a single molecule will provide sufficient sensitivity or specificity to be used as a stand-alone biological sentinel (discussed in (9)). Rather, it is more probable that next-generation diagnostic/prognostic tools will be based on the observation of a multiple candidates. In order to meet this goal, it is necessary to first define likely markers and the work performed by Topal et al. (6) provides more evidence to support a role for UCN2 in systolic dysfunction. Further work is now required to assess how UCN2 fits into the heart disease puzzle.

Address for Correspondence/Yazışma Adresi: Dr. Joseph V. Moxon, Vascular Biology Unit, School of Medicine and Dentistry James Cook University, Douglas Townsville, QLD 4811-*Australia* Phone: +61 (0)7 4781 4109 Fax: +61 (0)7 4781 3652 E-mail: joseph.moxon@jcu.edu.au

Accepted Date/Kabul Tarihi: 10.01.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 26.01.2012

doi:10.5152/akd.2012.037

Joseph V. Moxon, Theophilus I. Emeto, Jonathan Golledge
Vascular Biology Unit, School of Medicine and Dentistry,
James Cook University, Douglas, Townsville,
QLD 4811, Australia

Conflict of interest: None declared.

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 corticotrophin-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 USA 2001; 98: 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 USA 2001; 98: 7570-5. [CrossRef]
4. 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]
5. Emeto TI, Moxon JV, Rush C, Woodward L, Golledge J. Relevance of urocortins to cardiovascular disease. J Mol Cell Cardiol 2011; 51: 299-307. [CrossRef]
6. Topal E, Yağmur J, Otlu B, Ataş H, Cansel M, Açıkgöz N, et al. Relationship of urocortin-2 with systolic and diastolic functions and coronary artery disease: an observational study. Anadolu Kardiyol Derg 2012; 12: 115-20.
7. 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]
8. 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]
9. Moxon JV, Parr A, Emeto TI, Walker P, Norman PE, Golledge J. Diagnosis and monitoring of abdominal aortic aneurysm: Current status and future prospects. Curr Probl Cardiol 2010; 35: 512-48. [CrossRef]

Prof. Dr. Şahin Koçak'ın
Karagöz Akademisi isimli kitabından