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The value of urotensin II in patients with left-sided rheumatic valvular regurgitation

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Abstract *Aims:* Rheumatic valve diseases are most common etiological valve diseases in developing countries. Urotensin II is cardiovascular autacoid/hormone and may be associated with patients of heart valve diseases. The present study was to measure plasma urotensin II concentrations in patients with left-sided rheumatic valve diseases such as mitral regurgitation (MR) and aortic regurgitation (AR), and to examine its correlation with severity of valve impairment, function (New York Heart association, NYHA) class and pulmonary artery pressure (PAP).

Methods and results: Sixty patients with moderate to severe rheumatic left-sided valve regurgitation and 20 healthy controls were selected after performing the echocardiography. Plasma urotensin II level was measured in all subjects. The patients with MR and AR were significantly increased of left ventricular end diastolic dimension (LVEDD), left ventricular end systolic dimension (LVESD), left atrial diameter, PAP, but decreased of EF% versus the controls. Urotensin II level was highly significant in patients with MR (1.83 ± 0.92 ng/ml, $P < 0.001$) and AR (0.79 ± 0.3 ng/ml, $P < 0.05$) versus the controls (0.48 ± 0.13 ng/ml). Also, there was significant correlation between Urotensin II level and LVEDD (MR, $r = 0.318$, $P = 0.03$; AR, $r = 0.805$, $P < 0.001$), LVESD (MR, $r = -0.271$, $P = 0.115$; AR, $r = 0.614$, $P = 0.001$), and PAP (MR, $r = 0.706$, $P < 0.001$; AR, $r = 0.129$, $P = 0.538$).

Conclusion: Urotensin II was elevated in patients with rheumatic left-sided valvular regurgitation, and positively correlated with increased LVEDD (in both MR and AR), LVESD (only AR) and pulmonary artery pressure (only MR). Therefore, urotensin II level may be used as diagnostic biomarker in patients with rheumatic valvular diseases for assessment of the severity in parallel with echocardiography.

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1. Introduction

Human urotensin II is an 11 amino acid cyclic peptide and is expressed in most tissue organs of body including the heart and blood vessels, suggesting that urotensin II has a role in cardiovascular diseases[1]. Human urotensin II is the most potent vasoconstrictor, and more potent than endothelin-1 and acts through a G-protein-coupled receptor.[1,2] Urotensin II and urotensin II receptor are up-regulated in a number of cardiovascular disease states, implicating the urotensin II system in the pathogenesis and progression of cardiovascular diseases.[3]

Urotensin II has pleiotropic effects within the cardiovascular system, with evidence for modulation of cardiac contractility, vascular tone, cell proliferation, and cell growth. Recent studies have suggested that urotensin II may have a protective effect on the cardiovascular system, while others implicate urotensin II as a harmful mediator.[4] Evidence suggests that the condition of the vascular endothelium is a key determinant in how the cardiovascular system responds to urotensin II.[1,4]

In the developing countries of the world, rheumatic fever and rheumatic valve disease (RVD) remain among significant medical and public health problems.[5–7] Considerable numbers of young adults are in need of valve surgery. The primary consideration in management of adults with valvular heart disease is symptom status, emphasizing the importance of the clinical history. Besides assessment of valve anatomy, careful monitoring of symptoms due to chronic rheumatic valve disease is important during follow-up.[6]

Furthermore, echocardiographic screening of asymptomatic patients who have severe rheumatic valve disease remains the best tool for risk stratification and surgical indication. Attentive echocardiographic evaluation for objective signs of severity and complications of valve disease is recommended for patients with doubtful symptoms.[7,8]

Recently, the chronic phase of RVD is associated with ongoing plasma inflammatory mediators (e.g. atrial and brain natriuretic peptides) which correlate strongly with the severity of valve involvement, valve scarring, subsequent valve calcification and decreasing NYHA class.[8]

Many studies have been performed on the cardiovascular relation of urotensin II and documented elevated plasma urotensin II level in congestive heart failure,[9–11] coronary artery disease[2,3,12] and hypertension.[1] However plasma urotensin II level in subjects with the rheumatic valve disease is not yet clear.[13] Urotensin II is mainly regarded as a cardiovascular autacoid/hormone; it might have a pathophysiological role in rheumatic valve disease.

The present study was to measure plasma urotensin II concentrations in patients with rheumatic mitral or aortic regurgitation and to examine its correlation with severity of valve impairment, function (NYHA) class and pulmonary artery pressure.

2. Subjects and methods

2.1. Subjects

This study was performed in patient at cardiology department of Menoufia University Hospital and Police Academy Hospital and Nasser Institute Hospital, Cairo, Egypt, from March 2011 to December 2015.

A written informed consent, full history taking, and complete general and local examination of the heart, chest and abdomen, electrocardiography (ECG), full echo-doppler study and blood sample for plasma urotensin-II concentration were performed for all subjects.

The patients with isolated rheumatic mitral ($n = 35$) and aortic ($n = 25$) valve regurgitation and another healthy controls ($n = 20$) after performing echocardiography were selected in this study.

Exclusion criteria: Any concomitant valve lesion other than mitral and aortic valves, more than mild mitral stenosis, ischemic heart disease, severe systolic heart failure and any other congenital heart disease.

2.2. Methods

2.2.1. Echocardiographic study

Full M-mode, 2-D and Doppler echocardiographic study was done to all patients included in the study using GE vivid III echocardiography machine; 4-chamber, 5-chamber and 2 chamber apical views were obtained. Parasternal long and short axis views were also obtained.

2.2.2. Plasma urotensin-II measurement

Blood samples were collected into tubes containing EDTA and aprotinin (0.6 TIU/mL of blood). Then, plasma was stored at −70 °C until the day of the assay. Human plasma Urotensin II was measured by an enzyme-linked immunoassay (EIA) method. A specific and sensitive EIA kit was used for this assay (Phoenix Pharmaceutical Inc., California, USA).

2.3. Statistical analysis

Data of all patients were collected and analyzed using statistical package SPSS for PC version 16.5. Descriptive statistics were done using mean and standard deviation for continuous variables and percentage for categorical variables. Non-paired Student's *t*-test was done to find out the presence of significant difference between groups in continuous variables. Chi-square test was done to find out the presence of significant difference between groups in categorical variables. Pearson correlation coefficient was done to find out the presence of significant correlation between urotensin II and the different parameters. The P value < 0.5 was considered significant.

3. Results

3.1. Patients' demographic data

This study was performed on 35 patients with rheumatic mitral regurgitation and 25 patients with rheumatic aortic regurgitation and another 20 ages and sex matched healthy control group. The mean age of MR patients was 42 ± 4.2 years, 15 males (42.8%) and 20 females (57.2%). 20 patients (57.1%) had atrial fibrillation (AF), no one was in NYHA class I or IV but 18 patients (51.4%) had NYHA class II and 17 patients (48.6%) had NYHA class III. The mean age of the AR patients was 42.44 ± 3.1 years, 12 males (48%) and 13 females

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