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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 diseases¹. 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 Hospi-

tal 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

Table 1 General and demographic characteristics of all subjects.

	Mitral regurgitation <i>n</i> = 35	Aortic regurgitation <i>n</i> = 25	Healthy controls <i>n</i> = 20	<i>P</i> value
Age (mean ± SD)	42.06 ± 4.2	42.44 ± 3.1	42.45 ± 3.3	> 0.05 ^a > 0.05 ^b
<i>Sex</i>				
Males	15 (42.8%)	12 (48%)	9 (45%)	> 0.05 ^a
Females	20 (57.2%)	13 (52%)	11 (55%)	> 0.05 ^b
Sinus rhythm	15 (42.9%)	24 (96%)	20 (100%)	
Atrial fibrillation (AF)	20 (57.1%)	1 (4%)	0	NA
<i>NYHA class</i>				
I	0	0	0	NA
II	18 (51.4%)	2 (8%)	0	NA
III	17 (48.6%)	10 (40%)	0	NA
IV	0	13 (52%)	0	NA

NA: Not Applicable.

^a Mitral regurgitation versus normal patients.

^b Aortic regurgitation versus normal patients.

(52%). Only 1 patient (4%) had atrial fibrillation (AF), no one was in NYHA class I or IV but in 11 patients, 44% had NYHA class II and 14 patients (56%) had NYHA class III. In the healthy control group, their mean age was 42.4 ± 3.3 years, 9 males (45%) and 11 females (55%). All patients of this group were in sinus rhythm and they were apparently healthy individuals. There was no significant difference between the MR or AR and control groups regarding their mean age or their sex distribution ($P > 0.05$) (Table 1).

3.2. The echocardiographic study in all subjects

The left atrial dimension (LA), left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) and the pulmonary artery pressure (PAP), were significantly higher among MR or AR patient groups than those of the healthy controls ($P < 0.001$). Ejection fraction was significantly lower among the patients groups than that of the healthy controls ($P < 0.001$) (Table 2).

3.3. Plasma Urotensin II in all subjects

The mean Urotensin-II level was among the MR patients (1.83 ± 0.92 ng/ml, $P < 0.001$) and AR patients (0.79 ± 0.3 ng/ml, $P < 0.05$) versus 0.48 ± 0.13 ng/ml for the controls (Table 3).

3.4. Assessment Urotensin II in valve regurgitation

There was significant positive correlation of urotensin-II level with LVEDD ($r = 0.318$, $P = 0.03$) and PAP ($r = 0.706$, $P < 0.001$) in MR patients, but, there was no significant correlation with LVESD ($r = -0.271$, $P = 0.115$) (Table 4, Fig. 1). In AR patients, there was significant positive correlation of urotensin-II level with LVEDD ($r = 0.805$, $P < 0.001$) and LVESD ($r = 0.614$, $P = 0.001$). There was no significant correlation between urotensin level and the clinical or other echocardiographic parameters (Table 4, Fig. 1).

4. Discussion

Human urotensin II has several cardiovascular actions, including potent vasoactive, and cardiac inotropic and hypertropic properties.¹⁴ Altered plasma concentrations of urotensin II in diseases, such as heart failure, essential hypertension, renal disease, diabetes, and liver cirrhosis^{12,15} have raised the notion that urotensin II may be a useful biomarker in detecting disease onset or progression.¹⁶

The present study was conducted on patients with rheumatic mitral or aortic regurgitation versus healthy controls for clinical examination and echocardiographic assessment. Our results were in agreement with the study by Ozer et al.¹³ who studied 71 patients with RVD (mean age 40 ± 12 years, 17 female patients) and 25 normal subjects (mean age 40 ± 7 years, 8 female patients). They assessed their New York Heart Association (NYHA) functional class, RVD severity and pulmonary artery pressure (PAP), and measured plasma urotensin II levels. They found that urotensin II level was significantly higher in patients with rheumatic heart disease.

The present study showed that there was significant positive correlation between urotensin-II level, PAP, and LVEDD. These results were in agreement with the study by Ozer et al.¹³ who found that urotensin II was significantly correlated with mitral regurgitation ($r = 0.226$, $P = 0.02$), PAP ($r = 0.320$, $P = 0.01$), and NYHA class ($r = 0.213$, $P = 0.03$). There was positive correlation between urotensin II levels and severity of mitral regurgitation ($r = 0.248$, $P = 0.01$). In linear regression analysis, only PAP was predictive of urotensin II ($r = 0.3$; $P = 0.02$). They concluded that plasma urotensin II is elevated in chronic RVD, associated with severe mitral and tricuspid valve regurgitation. Furthermore, urotensin II level is correlated with NYHA functional class, and the increase in PAP is predictive of plasma urotensin II.

The LVEDD was found to be a predictive of urotensin II level in this study and these results were not in agreement with the results of Ozer et al.¹³ and this difference may be due that our patients had a more dilated LV dimensions and more impaired LV systolic function.

Table 2 Echocardiographic assessment in all subjects.

	Mitral regurgitation <i>n</i> = 35	Aortic regurgitation <i>n</i> = 25	Healthy controls <i>n</i> = 20	<i>P</i> value
LA (cm)	4.7 ± 0.6	3.4 ± 0.4	2.9 ± 0.2	< 0.001 ^a < 0.05 ^b
LVEDD (cm)	5.95 ± 0.5	6.1 ± 0.4	4.9 ± 0.35	< 0.001 ^a < 0.001 ^b
LVESD (cm)	3.94 ± 0.33	4.0 ± 0.34	3.0 ± 0.18	< 0.001 ^a < 0.001 ^b
EF (%)	57.83 ± 3.0	55.4 ± 3.1	64.8 ± 3.1	< 0.001 ^a < 0.001 ^b
PAP (mmHg)	45.0 ± 7.7	28.1 ± 5.6	23.9 ± 2.9	< 0.001 ^a < 0.05 ^b

PAP: pulmonary artery pressure, LA: left atrium, LVED: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, EF: Ejection fraction.

^a Mitral regurgitation versus normal patients.

^b Aortic regurgitation versus normal patients.

Table 3 Plasma urotensin-II levels in all subjects.

	Mitral regurgitation <i>n</i> = 35	Aortic regurgitation <i>n</i> = 25	Healthy controls <i>n</i> = 20	<i>P</i> value
Plasma Urotensin-II (ng/ml)	1.83 ± 0.92	0.79 ± 0.3	0.48 ± 0.13	< 0.001 ^a < 0.05 ^b

^a Mitral regurgitation versus normal patients.

^b Aortic regurgitation versus normal patients.

Table 4 Pearson correlation was measured between urotensin-II level and the different studied parameters among patients with mitral and aortic regurgitations.

	Mitral regurgitation <i>n</i> = 35		Aortic regurgitation <i>n</i> = 25	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Age	0.039	0.826	0.309	0.132
NYHA	0.199	0.251	-0.253	0.223
AF	-0.042	0.812	-0.117	0.578
LA	0.001	0.997	0.066	0.755
LVEDD	0.318	0.03**	0.805	0.0001**
LVESD	-0.271	0.115	0.614	0.001**
EF	0.015	0.931	-0.105	0.618
PAP	0.706	0.0001**	0.129	0.538
AR	-0.160	0.358		
MR			0.155	0.461

AF: Atrial fibrillation, PAP: pulmonary artery pressure, LA: left atrium, LVED: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, EF: Ejection fraction, MR: Mitral regurgitation, AR: Aortic regurgitation.

** *P* value is significant.

Our results were in agreement with the study^{17,18} that showed the expression of myocardial urotensin II in patients with heart failure. They found strong expression of urotensin II in the cardiomyocytes, and to a lesser extent in the vascular smooth muscle cells of patients with CHF. They also found that myocardial expression of urotensin II correlated significantly with LVEDD ($P = 0.0092$) and inversely with ejection

fraction ($P = 0.0002$). They suggested a possible role for urotensin II in the cardiac dysfunction and remodeling characteristic of CHF.

Also Quail et al.¹⁷ found that urotensin-II was an endogenous peptide upregulated in failing hearts. To date, insights into the myocardial actions of urotensin II have been obscured by its potent vasoconstrictor effects and interspecies differ-

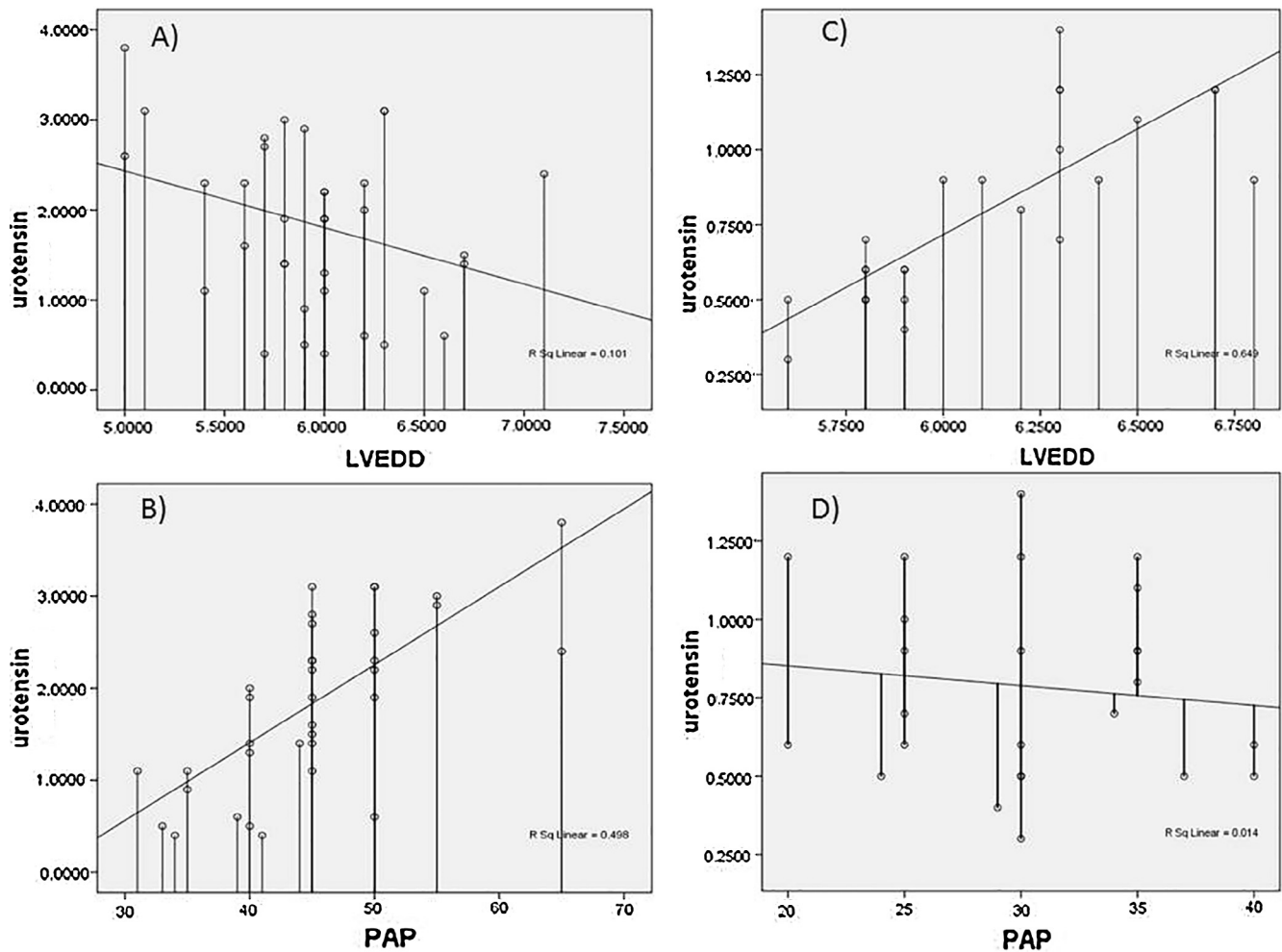


Figure 1 Linear regression analysis of the multiple echocardiographic factors that predict elevated urotensin II level in mitral regurgitation (MR) (A, B) and aortic regurgitation (AR) (C, D) with left ventricular end diastolic dimension (LVEDD) (A, C) and pulmonary artery pressure (PAP) (B, D).

ences in physiological responses to urotensin II. They examined the direct effects of exogenous urotensin II on in vitro contractility in nonfailing and failing human myocardial trabeculae. They found that urotensin II modulates contractility independent of vasoconstriction with opposite effects in failing and nonfailing hearts. Positive inotropic responses to urotensin II alone suggest that increased endogenous urotensin II constrains contractility in failing hearts via an autocrine and/or paracrine mechanism.¹⁸ These findings support a potential therapeutic role for urotensin II in heart failure.

Our results showed that pulmonary hypertension was a strong predictor of urotensin II level and this could be explained by that urotensin II was quickly revealed to be a very potent vasoconstrictor. The action of urotensin II was found to be independent of endothelial cells and to work via mobilization of intracellular calcium as well as through stimulation of extracellular calcium influx.¹⁹

As aforementioned, the actions of urotensin II in the pulmonary circulation are quite variable.¹⁹ These variations at different levels of the pulmonary circulation make it difficult to understand the role of urotensin II in pulmonary hypertension.

4.1. Conclusion

The present study indicates that urotensin II level may have a diagnostic of severe rheumatic valve regurgitation and can be used to follow up as a prognostic role in the pathophysiology of rheumatic heart disease and myocardial damage associated with valvular affection. This study consisted of relatively small number of patients. So it is recommended to have further studies with larger groups of patients to assess the relation between urotensin II and severity of all valvular lesions.

Conflict of interest

We have no conflict of interest to declare.

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