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Elevated uric acid and functional mitral regurgitation in dilated cardiomyopathy

M.V. YAZICIOĞLU, A. AVCI, G. AÇAR, Ö. ESEN[1], O. KARACA, G. ALICI, B. ÖZKAN, E. ALIZADE, M. BULUT, M. AKÇAKOYUN, A.M. ESEN

Department of Cardiology, Kartal Kosuyolu Yuksek Ihtisas Heart-Education and Research Hospital, Istanbul, Turkey
[1]Department of Cardiology, Memorial Hospital, Istanbul, Turkey

Abstract. – BACKGROUND: Recent findings suggest that there is a close relationship between chronic heart failure and uric acid.

AIMS: The aim of the study was to assess whether increased uric acid levels in patients with dilated cardiomyopathy might correlate with the degree of functional mitral regurgitation (MR).

MATERIALS AND METHODS: Sixty two consecutive patients diagnosed with dilated cardiomyopathy were included in the study. The patients were classified according to severity of functional MR into two groups: mild-moderate functional MR (ERO < 0.2 cm^2) and severe functional MR.

RESULTS: The patients with severe functional MR had significantly higher serum uric acid levels compared to patients without severe functional MR (6.34 ± 1.61 mg/dL vs 5.43 ± 1.17 mg/dL respectively, p = 0.012). Furthermore, tenting area, an important predictor of functional MR severity, was moderately correlated with the serum uric acid levels (r = 0.351, p = 0.005). It was also shown that the serum uric acid concentrations were inversely correlated with left ventricular (LV) ejection fraction, and positively correlated with LV volumes. There was also a significant relation between the serum uric acid and left atrial volumes and also brain natriuretic peptide (BNP) levels.

CONCLUSIONS: In conclusion, this study demonstrates that elevated serum uric acid levels in patients with dilated cardiomyopathy are correlated with the severity of functional MR and echocardiographic volume indices.

Key Words:
Cardiomyopathies, Dilated, Uric acid, Mitral regurgitation.

Introduction

Idiopathic dilated cardiomyopathy (IDC) is a primary myocardial disease of unknown cause characterized by left ventricular (LV) or biventricular dilatation and impaired myocardial contractility[1]. Functional mitral regurgitation (FMR) is a consistent finding in dilated heart failure, leading to a vicious cycle of ventricular and atrial overload, increase in pulmonary wedge pressure and congestive symptoms[2-4]. Once established, depending on its severity, FMR can further reduce the effective stroke output of the failing left ventricle, give rise to further activation of vasoconstrictor systems to maintain homeostasis. And also, activation of the renin-angiotensin-aldosterone system, the sympathetic nervous system, and increases in circulating catecholamine levels all may increase oxidative stress[5]. Dilated heart failure is a state of chronic deterioration of oxidative mechanisms resulting from enhanced oxidative stress and consequent subcellular alterations. In this circumstance, oxidant-producing enzymes, in particular xanthine oxidase (XO), the major cardiovascular source of reactive oxygen species, are up-regulated. Recent findings suggest that there is a close relationship between chronic heart failure and uric acid (UA)[6-8]. The elevated serum UA levels may reflect increased XO pathway activity and in turn the formation of superoxide and resultant oxidative stress via the XO system[9]. Thus, we hypothesized that there would be a relationship between UA, which is a marker of impaired oxidative metabolism, and degree of FMR which could cause an increase in oxidative stress due to hemodynamic deterioration and neurohormonal activation. Therefore, our aim was to assess whether increased UA levels in patients with dilated cardiomyopathy might correlate with the degree of FMR.

Patients and Methods

Study Population

Sixty two consecutive patients in stable clinical status followed in the Outpatient Clinic setting were studied. Each patient had a diagnosis of chronic heart failure due to IDC with LV ejection fraction ≤ 45% and duration of heart failure of at

Corresponding Author: Göksel AÇAR, MD; e-mail: gokselacar81@hotmail.com

least 3 months, was on standard therapy for heart failure and on optimal diuretic dose. The main exclusion criteria were (1) the presence of clinical or echocardiographic evidence of other cardiac diseases, such as organic valvular, ischemic, pericardial, congenital, or infiltrative heart disease; (2) structural mitral lesions, such as valve prolapse or rheumatic disease; (3) more than mild aortic regurgitation, (4) suboptimal echocardiographic windows, leading to incomplete quantification of FMR or anatomic assessment; and (5) atrial fibrillation or flutter. We also excluded several reasons that may affect the serum UA levels, including renal (serum creatinine level < 2 mg/dL) and hepatic dysfunction, chronic lung disease, hemolytic disorders, malignancies and concomitant inflammatory diseases such as infections and autoimmune disorders. None of the patients were on hypouricemic medication. On the day of the study, fasting venous blood samples were drawn from antecubital vein for routine laboratory tests, including serum UA. Serum concentrations of UA and other biomarkers were determined using commercial kits and an automated biochemical analyzer (Hitachi 747; Roche Diagnostics, Mannheim, Germany). All patients gave written, informed consent and the study was approved by the local Ethics Committee.

Echocardiographic Measurements

Transthoracic echocardiography was performed with patients in the left lateral decubitus position with a 2.5-3.5 MHz phased-array transducer probe (Vingmed System 3; GE Vingmed, Horten, Norway). All echocardiographic parameters were measured off-line, and an average of 3 cardiac cycles was used. LV ejection fraction (EF), end-diastolic (EDV) and end-systolic (ESV) volumes were calculated using Simpson's modified biplane method[10]. Left atrial (LA) volume was measured by the biplane area-length method from apical 2- chamber and 4-chamber views when the LA area was maximal during end systole. Severe FMR was defined as Effective Regurgitant Orifice area (ERO) ≥ 0.2 cm^2 as measured by the proximal isovelocity surface area (PISA) method[11]. The patients were classified according to severity of FMR into two groups: mild or moderate FMR (ERO < 0.2 cm^2, n = 35) and severe FMR (ERO ≥ 0.2 cm^2, n = 27). And also, mitral tenting area, as a well-established determinant of larger ERO[12], was used as an index of FMR. Tenting area was measured as an area enclosed between leaflets and annular plane of mitral valve at mid-systolic parasternal long-axis view as described previously[13]. In patients with no or trace FMR by color Doppler, tenting area was used as calculated, and ERO was assumed as null.

Statistical Analysis

Results are presented as mean ± SD, or frequency expressed as a numbers of patients (percentages). Comparison between groups with and without severe FMR was performed by means of unpaired Student's *t*-test for continuous variables and Mann-Whitney test was used for non-normally distributed continuous variables. An X^2 test or Fisher exact test was used for categorical data analyses, where appropriate. Pearson correlation tests were used to examine correlations between serum UA levels, clinical and echocardiographic variables. All of the statistical analysis was done using SPSS software (SPSS Inc. 16.0, Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

Results

The study included 62 patients with IDC in sinus rhythm. The patients were predominantly male (63%) and had a mean age of 49 ± 13 years. Two patients (3%) were in New York Heart Association (NYHA) functional class I, 39 (63%) in NYHA class II, 19 (31%) in NYHA class III, and 2 (3%) in NYHA class IV. Most patients (86%) were taking an angiotensin-converting enzyme (ACE) inhibitor. The remaining patients were on an angiotensin II receptor blocker due to ACE inhibitor intolerance. Eighty-six percent of patients were taking a diuretic and 79% a β-blocker. Thirty five patients (57%) presented with mild or moderate regurgitation and 27 patients (43%) with severe FMR. All of them had LV systolic dysfunction EF 31 ± 6%, (range 17%-44%). The mean LV end-systolic and end-diastolic volumes were: 140 ± 52 ml and 201 ± 65 ml, respectively. Mean LA volume was 78 ± 38 ml. The clinical and echocardiographic parameters of both groups are compared in Table I. The patients with severe FMR had significantly higher NYHA functional class and serum BNP (brain natriuretic peptide) level with respect to the patients without severe regurgitation (p < 0.001). The remaining clinical variables were similar between the groups. However, as a notable exception, serum UA levels differed significantly between patients with and without a severe FMR (6.34 ± 1.61 mg/dL vs 5.43 ± 1.17 mg/dL respectively, p = 0.012) (Figure 1). The patients with severe FMR had lower EF, higher EDV, ESV, LA

Table I. Clinical and Echocardiographic variables of the study population (n = 62)

	Mild/Moderate FMR ERO < 0.2 cm², n = 35)	Severe FMR (ERO > 0.2 cm², n = 27)	*p* value
Baseline clinical characteristics			
Age (years)	47 ± 12	51 ± 15	0.26
Male gender (%)	19 (54%)	18 (67%)	0.32
BSA (m^2)	1.83 ± 0.18	1.82 ± 0.17	0.80
NYHA class	2.0 ± 0.34	2.8 ± 0.58	< 0.001
SBP (mm Hg)	129 ± 20	123 ± 14	0.17
BNP (pg/mL)	149 ± 238	637 ± 596	< 0.001
Creatinine (mg/dL)	0.88 ± 0.18	0.99 ± 0.22	0.08
Uric acid (mg/dL)	5.43 ± 1.17	6.34 ± 1.61	0.012
ACE inhibitors/ARB	35 (100%)	27 (100%)	1
β-receptor blockers	27 (77%)	22 (81%)	0.68
Diuretics	30 (86%)	23 (85%)	0.95
Echocardiographic measurements			
LVEF (%)	33 ± 7	29 ± 5	0.002
LVEDV (mL)	177 ± 50	232 ± 69	< 0.001
LVESV (mL)	120 ± 43	166 ± 52	< 0.001
LAV (mL)	56 ± 18	108 ± 37	< 0.001
Tenting area (cm^2)	2.85 ± 0.96	4.53 ± 1.11	< 0.001

FMR: functional mitral regurgitation, ERO: effective regurgitant orifice area, BSA: body surface area, SBP: systolic blood pressure, BNP: B-type natriuretic peptide, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker; LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end diastolic volume, LAV: left atrial volume.

volumes and tenting area (Table I). Furthermore, tenting area, as an important predictor of FMR severity, was moderately correlated with the serum UA levels (r = 0.351, $p = 0.005$) (Figure 2). And also, by performing univariate correlation analysis, we found that the serum UA concentrations were inversely correlated with LV ejection fraction, and positively correlated with LV volumes (Table II). There was also a significant relation between the serum UA and LA volumes and also BNP levels, as indices of atrial and ventricular overload, in patients with dilated heart failure (Table II).

Discussion

The present study shows that high levels of serum UA are associated with severity of FMR in clinically well-matched patient groups with dilated heart failure. Furthermore, tenting area, as an index of severity of regurgitation, was significantly correlated with the serum UA concentrations. The association between hyperuricemia and chronic heart failure has long been recognized, but the exact mechanism for this association is not fully elucidated. A previous study[6] has shown that compared to age-matched controls, patients with chronic heart failure are hyperuricemic, independent of the effects of diuretics, renal impairment and other metabolic factors which are known to cluster with hyperuricemia. Moreover, coronary artery-to-coronary sinus gradients of UA concentrations have been demonstrated to occur in patients with chronic myocardial ischemia[14], which is consistent with the showing of a net release of UA in the coronary sinus following coronary artery angioplasty in patients with coronary heart disease[15]. Furthermore, higher serum UA level in the coronary sinus than in the aorta was reported in the patients with chronic heart failure[16]. These

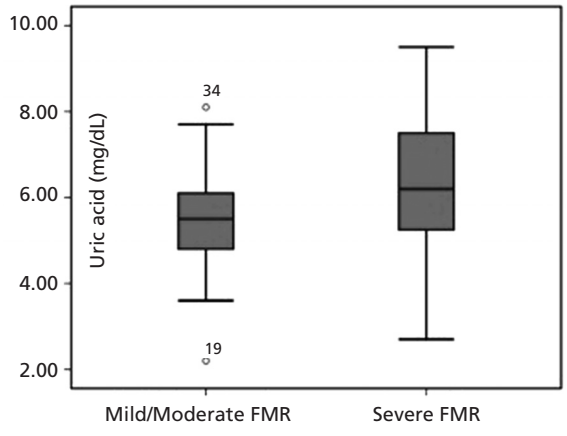

Figure 1. Serum uric acid levels in patients with mild-moderate functional mitral regurgitation (ERO < 0.2) and severe functional mitral regurgitation (ERO ≥ 0.2 cm^2).

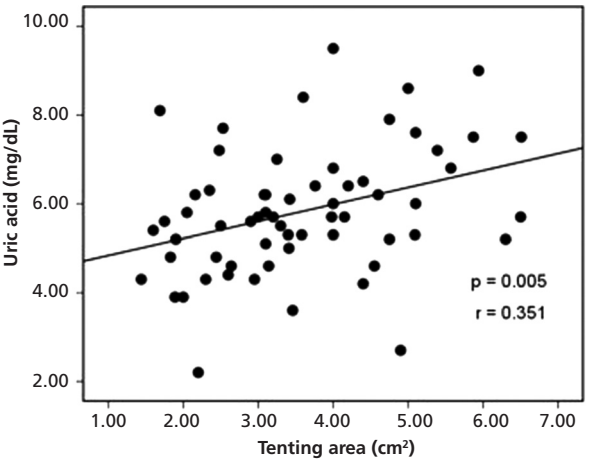

Figure 2. Correlation between serum uric acid level and mitral tenting area in 62 patients with dilated heart failure.

findings, together with the fact that XO is present in the human heart[17, 18]; suggest that, increased UA production in the heart contributes to elevations in serum UA concentration in patients with chronic heart failure. Several previous studies have shown that the serum UA levels were significantly related with the LV systolic[16] and diastolic dysfunction[19], and also measures of chronic inflammation[20] in patients with chronic heart failure. In their follow-up study by Niizeki et al[21] showed that the highest quartile of uric acid level was associated with the highest risk of cardiac events (a 4.45-fold increase) in 247 elderly heart failure patients. In their recent study Kim et al[22], followed 122 patients with nonischemic cardiomyopathy and demonstrated that even when compared to NT-proBNP, uric acid remained the only independent predictor for prognosis. In the present study, we found a significant association between serum UA and markers of systolic function or LV volumes, in agreement with the previous findings[16]. This may support the possibility that XO is activated, especially in severe chronic heart failure, and contributes to cardiac dysfunction. On the other hand, LA volumes, as an important determinant of mitral annular area, were well correlated to the severity of FMR[23], and also may be considered a morphologic indicator of increased LV filling pressure[24]. We also demonstrated that patients with severe FMR had significantly higher LA volumes with respect to the patients without severe regurgitation. Especially as an important finding, we showed a close relationship between LA volumes and serum UA levels. This is consistent with demonstration of a well correlation between increased BNP levels which is an adaptive response to increased ventricular filling pressures[25], and serum UA. Our results support the findings from a previous report[26] that showed an association between the elevated levels of serum UA and impaired hemodynamics. A possible explanation for our data may relate to impaired hemodynamic as consequence severe FMR, which is not only leading to a vicious cycle of ventricular and atrial overload[2-4], but also could cause an increase in oxidative stress due to hemodynamic deterioration and neurohormonal activation.

This study was designed to assess the relationship between UA and FMR but lacks follow-up data that would further elucidate potential mechanisms by which UA contribute to increased mortality in chronic heart failure. Morever, our results are observational and the observed association does not imply causation.

Table II. Univariate Pearson correlation coefficients for uric acid and patients characteristics in the study population (n = 62)

Variable	r	*p* value
LVEF (%)	- 0.334	0.008
LVEDV (mL)	0.254	0.046
LVESV (mL)	0.309	0.014
LAV (mL)	0.354	0.005
BNP (pg/mL)	0.364	0.004
Tenting area (cm^2)	0.351	0.005

LVEF: left ventricular ejection fraction, LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end diastolic volume, LAV: left atrial volume, BNP:B-type natriuretic peptide.

Conclusions

We have demonstrated that elevated serum UA levels in patients with dilated heart failure are strongly related to severity of FMR. Although further studies are needed to determine whether such a relationship is causal, the finding from the present study may provide further insights into the mechanism underlying the pathogenesis of observed association between UA and increased mortality in patients with chronic heart failure.

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