ABSTRACT

Objectives: Elevated uric acid levels are associated with diastolic dysfunction in chronic heart failure patients. Uric acid is a marker of impaired oxidative metabolism and is correlated with endothelial function. In this study, we investigated whether uric acid levels correlate with the degree of left ventricular diastolic dysfunction (LVDD) in patients with normal ejection fraction.

Design: Prospective case-control study

Subjects and Methods: Uric acid levels were measured in 201 patients with normal ejection fraction. The study population was divided into two groups as controls and patients with LVDD. Patients with LVDD were divided into two groups according to dysfunction grade. (Normal, n = 64, Grade 1 LVDD, n = 74, Grade 2 LVDD, n = 63).

Interventions: For uric acid analysis, 5 ml of venous blood was drawn from each patient after at least 8 hours of fasting.

Main Outcome Measures: Serum uric acid levels were measured and LVDD was assessed by transthoracic echocardiography

Results: Uric acid levels were significantly lower in the normal diastolic function group than grade 1 LVDD and grade 2 LVDD groups respectively (4.28 ± 1.20 mg/dl, 8.17 ± 2.12 mg/dl, 9.52 ± 2.30 mg/dl, p < 0.001). Although Grade 2 LVDD patients had higher uric acid levels, there is no significant difference between grade 1 and grade 2 LVDD.

Conclusions: Our study demonstrated that uric acid level was significantly elevated in patients with diastolic dysfunction. Further studies are needed to assess whether inhibition of xanthine oxidase (XO) with allopurinol results in an improvement in diastolic dysfunction.

INTRODUCTION

Some studies suggest that uric acid (UA) is potentially an independent risk factor for both cardiovascular disease and kidney disease[5-7]. Other studies have noted that the development of hypertension, obesity, kidney disease, and diabetes can be predicted by an elevated level of UA[5–12]. A strong relation between hyperuricemia and subsequent cardiovascular disease risk in unselected populations has been identified by epidemiological studies[13-15].

The mechanisms by which UA may engender organ damage is still incompletely understood, but there is increasing evidence that endothelial dysfunction is a fundamental mechanism whereby this substance may affect cardiovascular and renal function and structure[16].

Reduced bioavailability of nitric oxide (NO), which normally mediates local vasodilatation, inhibits platelet aggregation, and reduces local vascular inflammation, lead to endothelial dysfunction[17]. Cardiovascular disease can be predicted by endothelial dysfunction and it is central to the development and progression of atherosclerosis[18,19]. An inverse relationship between serum UA concentration and NO activity has been identified and therefore it is possible that UA directly influences endothelial dysfunction[20].

NO has been reported to exert significant effects on the relaxation phase of cardiac contraction, in
some cases even in the absence of changes in systolic function. NO selectively induce an earlier onset of isometric relaxation without affecting the rate of isometric tension development[21].

Previously, it was demonstrated that elevated UA levels are associated with diastolic dysfunction in chronic heart failure patients[22].

In this study, we investigated whether UA levels correlated with the degree of left ventricular diastolic dysfunction (LVDD) in patients with normal ejection fraction.

SUBJECTS AND METHODS

Study population

A total of 201 outpatient subjects with normal ejection fraction were studied between August 2012 and August 2013. Transthoracic echocardiography (Vivid 7, Vingmed Ultrasound, GE, Horten, Norway) was performed in the left lateral decubitus position. Pulse Wave (PW) Doppler mitral filling flow velocities (Em and Am waves) and the E/A ratio were calculated. Apical four chamber view of mitral annular tissue, Doppler and PW Doppler measurements taken with the Em and Am-wave velocities and mitral ‘e’ values were calculated for each patient. All measurements were made according to the recommendations of the American Echocardiography Society[23]. Normal diastolic function was described as E/A > 1, lateral e’> 8, grade 1 diastolic dysfunction was described as E/A < 1, lateral ‘e’ ≤ 8, grade 2 diastolic dysfunction was described as E/A > 1 and lateral e’ ≤ 8. We also described normal ejection fraction (EF) as > 50%[23].

After echocardiography examinations, the study population was divided into two groups: control group with normal diastolic function and patient group with diastolic dysfunction. Patients with diastolic dysfunction were further divided into two groups according to dysfunction grade. (Normal, n = 64, Grade 1 LVDD, n = 74, Grade 2 LVDD, n = 63).

We excluded patients with gout, usage of XO (xanthine oxidase) inhibitors, atherosclerotic heart disease (acute coronary syndromes, and stable coronary heart disease), a history of smoking, cerebrovascular disease within the last three months, obstructive or non-obstructive hypertrophic cardiomyopathy, severe arrhythmias, uncorrected congenital heart disease, active perimyocarditis, usage of thiazide diuretics, chronic renal disease and diabetic nephropathy.

Serum blood urea nitrogen (BUN), serum creatinine and UA were measured in the routine laboratory by an automated technique using an auto analyzer after at least 8 hours of fasting. The blood plasma uric acid level between 3.6 mg/dl (~ 214 µmol/l) and 8.3 mg/dl (~ 494 µmol/l) (1 mg/dl = 59.48 µmol/l) was taken as the normal reference range for this study.

Statistical Methods

Data analysis was performed using SPSS for Windows 15.0 (Statistical Package for Social Science, SPSS inc., Chicago, IL, U.S.). Descriptive statistics were expressed as mean ± standard deviation. For the comparison of the averages of the two groups, we used t-test. We assessed the linear relationship between two variables with Pearson’s (for normally distributed data) and Spearman’s (for abnormally distributed data) correlation coefficient. For comparison of numerical data between groups, “one-way ANOVA” test and for multiple comparisons the “post-hoc Tukey’s HSD” test were used. Finally, the relationship between clinical and demographical parameters (including serum UA) and diastolic dysfunction was analyzed by linear regression analysis. In the statistical analysis, p < 0.05 was considered statistically significant.

RESULTS

Clinical and echocardiographical parameters are shown in Table 1. The mean age of controls, grade 1 LVDD group and grade 2 LVDD group was 49.30 ±

<table>
<thead>
<tr>
<th>Clinical and echocardiographical variables</th>
<th>Normal (n : 64)</th>
<th>Grade 1 DD (n : 74)</th>
<th>Grade 2 DD (n : 63)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.30 ± 10.99</td>
<td>64.22 ± 10.63</td>
<td>63.73 ± 10.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (female %)</td>
<td>48.5</td>
<td>52.2</td>
<td>55.3</td>
<td>0.898</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>26.7</td>
<td>25.8</td>
<td>27.3</td>
<td>0.864</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>26.51 ± 8.88</td>
<td>27.56 ± 10.13</td>
<td>32.63 ± 13.71</td>
<td>0.004</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.81 ± 0.19</td>
<td>0.85 ± 0.15</td>
<td>0.83 ± 0.17</td>
<td>0.359</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>4.28 ± 1.20</td>
<td>8.17 ± 2.12</td>
<td>9.52 ± 2.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral E wave (m/s)</td>
<td>0.72 ± 0.16</td>
<td>0.57 ± 0.15</td>
<td>0.84 ± 0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral A wave (m/s)</td>
<td>0.58 ± 0.12</td>
<td>0.87 ± 0.11</td>
<td>0.67 ± 0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.29 ± 4.16</td>
<td>63.02 ± 3.61</td>
<td>62.45 ± 8.26</td>
<td>0.051</td>
</tr>
<tr>
<td>LA diameter (cm)</td>
<td>3.12 ± 0.56</td>
<td>3.46 ± 0.40</td>
<td>3.70 ± 0.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mitral annulus ‘e’ (cm/s)</td>
<td>5.94 ± 1.01</td>
<td>6.00 ± 1.20</td>
<td>0.758</td>
<td></td>
</tr>
</tbody>
</table>

BUN: blood urea nitrogen, DD: diastolic dysfunction, LA: left atrium, LVEF: left ventricle ejection fraction
As shown in Table 2, serum uric acid levels correlated with age. LVDD grade, mitral A wave, left atrium (LA) diameter, LVEF, blood urea nitrogen (BUN) and creatinine (r = 0.422, p < 0.001; r = 0.717, p < 0.001; r = 0.263, p < 0.001; r = 0.440, p < 0.001; r = 0.218, p = 0.002; r = 0.175, p = 0.013; r = 0.178, p = 0.011, respectively). After multivariate linear regression analysis, age and uric acid were independent variables for diastolic dysfunction (β = 0.314, p < 0.001 and β = 0.157, p = 0.039, respectively, Table 3).

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>t</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.314</td>
<td>4.323</td>
<td>4.323</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.076</td>
<td>-1.052</td>
<td>-1.052</td>
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<tr>
<td>Uric acid</td>
<td>0.157</td>
<td>2.081</td>
<td>2.081</td>
</tr>
<tr>
<td>BUN</td>
<td>-0.117</td>
<td>-1.311</td>
<td>-1.311</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.124</td>
<td>1.238</td>
<td>1.238</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Our study is the first study, which compared the relationship between UA levels and diastolic dysfunction grade. Previous studies evaluated relationship between UA levels and systolic heart failure or idiopathic cardiomyopathy.[24]

High serum UA concentration as a marker of increased cardiovascular risk has been recognized as important for more than 50 years. The association between hyperuricemia and total cardiovascular mortality was statistically significant after multivariate adjustment.[25,26]

UA is a pro-oxidant that can increase oxygen radicals in circulation, which may in turn promote the lipid oxidation, leading to vascular endothelial dysfunction, inflammation, NO production impairment, atherosclerosis, and thrombogenesis[16].

Since xanthine oxidase (XO) generates UA from xanthine, UA could reflect underlying XO activity. In addition, XO is also known to produce oxidants. Thus, the presence of XO-associated oxidants could be simply reflected by an elevated UA, which may be eventually responsible for the endothelial dysfunction.[27]. The Framingham study showed that serum UA levels are an independent predictor of hypertension and progression to a higher BP stage. This may be related to activation of the renin-angiotensin system by UA.[28].

In healthy humans, there is an inverse circadian relationship between serum UA levels and NO. It is supporting the hypothesis that UA impairs endothelial function.[29].

Increased right and left atrial pressures among patients with ischemic heart disease or dilated cardiomyopathy in a small case series are some worse hemodynamic measures associated with hyperuricemia.[10,31].

The major physio-pathological mechanism for diastolic heart failure in hyperuricemia might be the relationship between NO and UA.[20]. In this present study, we demonstrated that UA levels were significantly increased in diastolic dysfunction group than control group. Furthermore, UA levels were increased in grade 2 diastolic heart failure group than grade 1 heart failure group, but there was no significant difference between both groups. The incidence of LVDD increases with age. Our diastolic dysfunction group had patients with older age than normal group. But after regression analysis, UA and age were independent factors for LVDD.

Effects of NO on left ventricle (LV) relaxation have been documented in the isolated ejecting buffer-perfused guinea pig heart, studied at constant preload, afterload and heart rate.[62]. An effect of NO and / or cGMP on twitch relaxation and diastolic properties has also been reported in isolated cardiac myocytes. The
NO or cGMP-induced increase in myocyte diastolic length, in the absence of changes in diastolic Ca++ , has been suggested to be due to an acute reduction in active diastolic tone, and is analogous to the changes in LV diastolic pressure–volume relations observed in clinical studies[30,34].

Previously, it was demonstrated that elevated UA levels are associated with diastolic dysfunction in chronic heart failure patients[22]. They found no correlation between uric acid and left ventricular volumes, ejection fraction, or stroke volume. In a multivariate model, uric acid predicted diastolic dysfunction independently of renal function, diuretic dose, and left ventricular volumes.

There is an important distinction between UA as a coincidental or causal risk factor because, if UA is causal, treatment to lower serum UA concentrations may potentially reduce cardiovascular disease risk[33]. Various clinical studies have shown that endothelial function in patients with diabetes, patients with coronary artery disease, smokers, and, in particular, patients with CHF have been improved by XO inhibition[30]. The primary effect of allopurinol could be the improvement in endothelial function that has resulted in better myocardial perfusion, thereby improving LV function. Alternatively, the improvement in endothelial function could be secondary to a direct effect of allopurinol on LV function through improvement in myocardial energetic efficiency and oxygen consumption[37].

CONCLUSION

Our study demonstrated that UA level was significantly elevated in patients with diastolic dysfunction and normal ejection fraction. UA levels also correlated with age. The incidence of LVDD increases with age. Our diastolic dysfunction group had older patients than in the control group. But after regression analysis, UA and age were independent factors for LVDD. Further studies are necessary to see improvement of diastolic functions using UA lowering drugs.

Limitations of Study

This study is a single-center, observational, and non-randomized study. We also did not evaluate NO activity, which was directly affected by UA. Further studies are needed to compare uric acid and LVDD at similar ages.

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Conflict of interest: None declared

REFERENCES


None declared


