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[Original Article]

URIC ACID INCREASES THE INCIDENCE OF VENTRICULAR ARRHYTHMIA IN PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

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Abstract : Backgrounds. Elevated uric acid (UA) level is reported to be related to the development of left ventricular hypertrophy (LVH) which is associated with high incidence of ventricular tachycardia (VT) and sudden cardiac death. However, little is known about the association between serum UA levels and the occurrence of VT. Thus, we examined the relationship between serum UA levels and the appearance of VT in patients with LVH. **Methods.** The study subjects consisted of 167 patients (110 males, mean age 67.4 ± 12.7 years) with LVH detected by echocardiography. These patients were divided into two groups based on whether VT was presented (defined by more than 5 beats, $n=27$) or not ($n=140$) by 24-hour Holter ECG monitoring. Left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVDd), the E/A ratio and deceleration time of transmitral flow velocity were assessed by echocardiography in each group. In addition, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), sodium, potassium, hemoglobin, total bilirubin and UA were compared in each group. **Results.** Echocardi ographic findings did not show the difference between the two groups. However, BUN and UA levels in the VT group were significantly higher than those in the Non-VT group ($p<0.01$). eGFR was significantly lower in the VT group than that in the Non-VT group ($p<0.01$). A multivariate logistic regression analysis identified the UA level as an independent predictive factor for the occurrence of VT (odds ratio 1.61, 95% confidence interval 1.1-2.2, $p<0.01$). **Conclusions.** These results suggest that serum UA level is a useful marker for predicting ventricular arrhythmias in patients with LVH.

Key words : Ventricular arrhythmia, Hypertension, Kidney

INTRODUCTION

Ventricular tachycardia (VT) leads to poor outcome in patients with cardiovascular disease. Therefore, an effective predictor is required to identify the incidence of VT. Although previous studies have shown effective predictors for the incidence of VT, the most useful predictor has not been elucidated.

Although serum uric acid (UA) is a common parameter obtained by routine laboratory testing, elevated concentrations of serum UA have been considered to be associated with cardiac events and total mortality, such as heart failure[1-3], myocardial infarction, angina pectoris[4-6] and atrial fibrillation (AF)[7,8]. Hyperuricemia is frequently encountered in hypertensive patients[9]. Some large studies have demonstrated that elevated concentrations of serum UA levels are related to the development of left ventricular hypertrophy (LVH) in essential hypertension[4,10], but the exact mechanisms have not been fully elucidated. On the other hand, LVH is

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recognized as one of the pivotal predictors of ventricular tachyarrhythmias and sudden cardiac death[11,12].

However, little is known about the relationship between serum UA levels and the occurrence of VT. Therefore, we investigated the association between serum UA levels and the occurrence of VT in patients with LVH.

MATERIALS AND METHODS

Study population and protocol

We analyzed data obtained in a total of 167 patients with LVH detected by echocardiography. All of the patients underwent medical investigation at Fukushima Medical University in Fukushima, Japan. This study was approved by the Ethics Committee of Fukushima Medical University Hospital, and written informed consent was obtained from all patients. LVH was defined as wall thickness of interventricular septum (IVST) and posterior wall (PWT) being greater than 12 mm by echocardiography. Patients with left ventricular ejection fraction (LVEF) less than 50%, myocardial infarction, chronic AF, valvular heart disease, and receiving hemodialysis were excluded. The patients were divided into two groups based on whether VT was presented (defined by more than 5 beats) or not by 24-hour Holter ECG monitoring. After recording 24-hour Holter ECG monitoring, venous blood samples were obtained from all of the patients at our hospital. All patients underwent electrocardiogram and a comprehensive echocardiographic study using commercially available ultrasound system. QRS duration and QTc interval were measured in electrocardiogram. LVEF, left ventricular end-diastolic diameter (LVDd), the E/A ratio and deceleration time (DcT) of transmitral flow velocity were assessed by echocardiography in each group. In addition, the following parameters were compared : blood urea nitrogen (BUN), creatinine, sodium, potassium, hemoglobin (Hb), total bilirubin (T-bil) and UA. To evaluate renal function correctly, estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation, applying coefficients corrected for the Japanese population based on the concentration of serum creatinine (SCr) [eGFR (ml/min/1.73 m^2)=$194\times SCr^{1.094}\times$age (years)$^{-0.287}$ ($\times$0.739, if female)][13].

Statistical analysis

Statistical analyses were performed with SPSS (version 17, SPSS Inc, Chicago, Illinois). Parametric data are presented as mean±SD. Patient correlation was applied to the regression analysis. Differences between the two groups were assessed by use of the unpaired Student's *t*-test for continuous variables, and Fisher's exact test for categorical variables. A value of $P<0.05$ was considered statistically significant. Univariate logistic regression analysis was performed to identify the association between the occurrence of VT and various parameters obtained in this study. Finally, multivariate logistic regression analysis was performed to determine an independent predictive factor for the occurrence of VT. Confidence interval (CI) is expressed as 95% CI.

RESULTS

Clinical, electrocardiographic, echocardiographic, and biochemical features

Baseline patient characteristics are shown in Table 1. The difference between the two groups was not statistically significant according to age, gender, hypertension, diabetes, dyslipidemia, and medication. At baseline, 86.8% of the study patients were taking antihypertensive drugs. β-blockers, calcium channel blockers, diuretics and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used for hypertension either alone or with various combinations in 31.7%, 56.3%, 28.7% and 64.1% of the study patients, respectively. Additional use of statin and allopurinol (UA-lowering medication) were 25.7% and 10.2%, respectively. Electrocardiographic, echocardiographic and biochemical features are shown in Table 2. There were no significant differences in electrocardiographic and echocardiographic features between the two groups statistically. The data of E/A ratio and DcT showed relaxation impairment (E/A=0.85±0.34, DcT=232.2±67.5 msec). In biochemical features, BUN and UA levels were significantly higher in the VT group than that in the Non-VT group ($P<0.01$). Estimated eGFR was significantly lower in the VT group than that in the Non-VT group ($P<0.01$).

Association between serum UA and the occurrence of VT

Association between the occurrence of VT and

Table 1. Baseline clinical characteristics

	VT (n=27)	Non-VT (n=140)	P value
Age	67.0 ± 13.0	69.8 ± 11.3	NS
Male (%)	22 (72%)	95 (68%)	NS
BMI (kg/m^2)	25.5 ± 1.0	24.2 ± 0.3	NS
Hypertension (%)	23 (85%)	122 (87%)	NS
Diabetes (%)	6 (22%)	24 (17%)	NS
Dyslipidemia (%)	7 (25%)	41 (29%)	NS
Medication			
β blockers (%)	9 (33%)	43 (31%)	NS
ACE-I/ARB (%)	21 (77%)	85 (61%)	NS
Ca channel blocker (%)	13 (48%)	80 (57%)	NS
Statins (%)	7 (25%)	31 (22%)	NS
Diuretics (%)	10 (37%)	38 (27%)	NS
Allopurinol (%)	2 (7%)	15 (11%)	NS

VT, ventricular tachycardia ; BMI, body mass index ; ACE-I, angiotensin-converting enzyme-inhibitors ; ARB, angiotensin II receptor blocker.

Table 2. Echocardiography and blood biochemical features

	VT (n=27)	Non-VT (n=140)	P value
Electrocardiographic findings			
QRS duration (msec)	102.0 ± 16.5	100.9 ± 15.7	NS
QTc interval (msec)	433.3 ± 34.8	421.5 ± 32.5	NS
Echocardiographic findings			
IVST (mm)	13.6 ± 2.1	13.7 ± 1.8	NS
PWT (mm)	13.3 ± 1.6	13.4 ± 1.3	NS
LVDd (mm)	46.6 ± 7.6	44.9 ± 6.1	NS
LVEF (%)	59.2 ± 11.1	60.8 ± 7.6	NS
E/A ratio	0.86 ± 0.29	0.85 ± 0.34	NS
DcT (msec)	225.6 ± 60.9	233.4 ± 67.4	NS
Blood biochemical findings			
Blood urea nitrogen (mg/dl)	23.4 ± 13.5	17.3 ± 8.3	P<0.01
Creatinine (mg/dl)	1.31 ± 1.12	1.02 ± 0.82	NS
Estimated GFR (ml/min/1.73 m^2)	53.6 ± 21.8	70.7 ± 27.8	P<0.01
Sodium (mmol/l)	139.4 ± 3.1	140.5 ± 2.7	NS
Potassium (mmol/l)	4.4 ± 0.4	4.2 ± 0.4	NS
Hemoglobin (g/dl)	12.2 ± 2.1	12.8 ± 1.9	NS
Total bilirubin (mg/dl)	0.65 ± 0.23	0.68 ± 0.41	NS
Uric acid (mg/dl)	6.8 ± 1.4	5.4 ± 1.5	P<0.01

IVST, interventricular septal thickness ; PWT, posterior left ventricular wall thickness ; LVDd, left ventricular internal dimension in diastole ; LVEF, left ventricular ejection fraction ; E/A, peak early diastolic left ventricular filling velocity/peak atrial filling velocity ; DcT, deceleration time.

various parameters obtained in this study by univariate logistic regression analysis are shown in Table 3. Electrocardiographic and echocardiographic features did not show the relationship with the occurrence of VT. In biochemical features, BUN, eGFR, and UA were significantly related to the occurrence of VT. Odds ratio (OR) of BUN, eGFR, and UA was 1.05, 0.98, and 1.78, respectively. To determine an inde-

Table 3. The relationship to the occurrence of VT in a univariate logistic regression analysis

	OR	95% CI	*P* value
QRS	1.00	0.97–1.03	NS
QTc	1.01	0.99–1.02	NS
IVST	0.96	0.85–1.09	NS
PWT	0.96	0.83–1.11	NS
LVDd	1.04	0.97–1.11	NS
LVEF	0.97	0.93–1.02	NS
E/A ratio	1.14	0.34–3.79	NS
DcT	0.99	0.99–1.01	NS
Blood urea nitrogen	1.05	1.01–1.09	$P<0.01$
Creatinine	1.37	0.94–1.98	NS
Estimated GFR	0.98	0.95–0.99	$P<0.01$
Sodium	0.87	0.76–1.00	NS
Potassium	2.61	0.88–7.67	NS
Hemoglobin	1.01	0.71–1.07	NS
Total bilirubin	0.82	0.25–2.64	NS
Uric acid	1.78	1.33–2.37	$P<0.01$

OR, odds ratio ; 95% CI, 95% confidence interval.

Table 4. The relationship to the occurrence of VT in a multivariate logistic regression analysis

	OR	95% CI	*P* value
Blood urea nitrogen	1.01	0.96–1.06	NS
Estimated GFR	0.99	0.96–1.01	NS
Uric acid	1.61	1.18–2.20	$P<0.01$

pendent predictive factor for the occurrence of VT, we next performed multivariate logistic regression analysis for BUN, eGFR, and UA (Table 4). The result of the analysis revealed that only UA level was an independent factor (OR, 1.61 ; 95% CI, 1.18 to 2.20 ; $p<0.01$).

We also analyzed the relation of VT with serum UA in male patients ($n=117$). Multivariate logistic regression analysis also revealed that UA level was an independent factor (OR, 1.55 ; 95% CI, 1.08 to 2.23 ; $p<0.01$) in male patients.

DISCUSSION

This is the first study which showed that elevated concentrations of serum UA had the strongest association with the occurrence of VT in patients with LVH. Patients with LVH are at increased risk of sudden cardiac death mainly caused by ventricular tachyarrhythmias. Thus, it is necessary to establish the most helpful predictor for the appearance of life-threatening ventricular tachyarrhythmias. In patients with LVH, some previous studies have shown effective predictors for the incidence of VT, such as prolonged QRS duration and QTc interval in electrocardiogram[14], LV systolic and diastolic dysfunction in echocardiography, worsening renal function in laboratory testing and others. However, little is known about the strongest predictive factor for the occurrence of VT. Therefore, we investigated a novel potential predictor for the appearance of fatal ventricular tachyarrhythmias.

Serum UA is a common parameter obtained by routine laboratory testing. It has been shown that elevated concentrations of serum UA levels are related to the development of cardiovascular diseases[15–17]. There are two major factors that increase concentrations of serum UA level. One is excretion disorder by renal dysfunction and the other is increased UA production by the activation of

the XO system[18]. This study showed that serum UA and renal dysfunction, such as BUN and eGFR, were related to the occurrence of VT by univariate logistic regression analysis. It is generally accepted that renal dysfunction increases concentrations of serum UA level. Additionally, there is convincing evidence that renal dysfunction is related to cardiac arrhythmia and sudden cardiac death[19-21]. Although we did not investigate the association between serum UA and renal dysfunction in this study, serum UA was the strongest relationship parameter to the occurrence of VT, independent of renal dysfunction by multivariate logistic regression analysis. Thus, we next considered the association between increased UA production by the activation of the XO system and the incidence of VT. Serum UA is a product in the terminal stage of purine metabolism produced via XO system activation. Many epidemiologic studies have suggested that elevated concentrations of serum UA via XO system activation is related to the generation of oxidative stress[22,23] and inflammatory mediators, such as tumor necrosis factor-alpha and mitogen-activated protein kinases[24-26]. Recent studies have demonstrated that oxidative stress and inflammatory mediators induce electrophysiological[27] and structural remodeling[7,10,28,29] in the atrial and ventricular myocardium. Letsas KP *et al.*[8] have recently reported that increased levels of UA are associated with the perpetuation of AF. They considered that inflammation and oxidative stress induced by UA were associated with the development of AF substrate. Therefore, we considered that LV myocardial damage induced by serum UA might be related to the occurrence of VT. In this study, LV dilatation, the degrees of LVH, and LV systolic and diastolic function were not related to the incidence of VT. To clarify detailed mechanisms for VT induced by high levels of serum UA, we should conduct an additional research.

Finally, if XO system activation has been related to the occurrence of VT, UA lowering treatment with XO inhibition may be effective against the occurrence of VT. XO activation can be inhibited by allopurinol. Therefore, it is possible that allopurinol is useful for upstream therapy in VT. Further investigation of the role of serum UA in patients with VT may lead to the development of effective therapeutic strategies.

LIMITATIONS

In our study, there were some limitations. First, our sample size was small. Second, the number of men was greater. It is known that UA level is associated with gender differences[10]. Further study with a large number of patients may resolve these limitations in the future.

CONCLUSIONS

The incidence of VT was related to serum UA level, but not to the degrees of LVH, and LV systolic and diastolic function. These results suggest that serum UA level is a useful marker for predicting ventricular arrhythmia in patients with LVH.

DISCLOSURES

None.

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