Relation of Elevated Serum Uric Acid Level to Endothelial Dysfunction in Patients with Acute Coronary Syndrome

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Aim: Serum uric acid (SUA) level is known to have a prognostic value in patients with acute coronary syndrome (ACS). Endothelial function plays an important role in the development of cardiovascular disease. Although relation between SUA level and endothelial function has been previously studied in various populations, it is partially understood in patients with ACS.

Methods: A total of 55 patients with ACS with measurements of SUA level and reactive hyperemia index (RHI) to evaluate endothelial function were included. They were classified into three groups according to the tertiles of SUA level. The tertiles of SUA level were as follows: low tertile, ≤ 5.2 mg/dl; intermediate tertile, 5.3 to 6.5 mg/dl; and high tertile, ≥ 6.6 mg/dl.

Results: Mean SUA level and RHI were 5.8 ± 1.5 mg/dl and 1.88 ± 0.58. There was a significant negative correlation between SUA level and RHI ($r = -0.41$, $p = 0.002$). RHI was stepwisely observed in favor of the higher tertile groups (2.14 ± 0.74 vs. 1.84 ± 0.45 vs. 1.67 ± 0.38, $p = 0.04$). Multivariate analysis showed elevated SUA level as an independent predictor of reduced RHI.

Conclusion: Elevated SUA level was significantly associated with endothelial dysfunction in patients with ACS, possibly leading to subsequent poor outcomes following ACS.

Key words: Uric acid, Endothelial function, Reactive hyperemia index, Acute coronary syndrome

Introduction

Several epidemiological studies have shown a relation between elevated serum uric acid (SUA) level and subsequent cardiovascular events, including coronary artery disease[1-3]. SUA level is also known to have a prognostic value in patients with acute coronary syndrome (ACS), especially ST-segment elevation myocardial infarction (MI)[4, 5]. In addition, our recent investigation suggested that patients with ACS with elevated SUA level had greater lipid content of coronary plaque in non-culprit lesions, assessed by integrated backscatter intravascular ultrasound (IB-IVUS)[6].

Previous reports have indicated that endothelial function plays an important role in the progression of coronary atherosclerosis[7, 8]. Significant relation between SUA level and endothelial function has been directly studied in patients with no overt cardiovascular disease[9, 10], metabolic syndrome including hypertension and diabetes[11], and chronic kidney disease[12], primarily assessed by flow-mediated dilation (FMD). Although endothelial function is also considered to play an important role in the development of cardiovascular disease in patients with ACS with higher SUA level, their direct relation has not been well evaluated. Reactive hyperemia index (RHI) has been recently shown to be a useful method in non-invasively and reproducibly evaluating peripheral endothelial function[13], which has been validated to indicate the risk for cardiovascular adverse events[14]. Additionally, RHI reportedly is operator-independent and easy to use compared with FMD[15], indicating that RHI presents an alternative to FMD. The aim of this study was to investigate the relation between SUA level and endothelial function assessed by RHI in patients with ACS.

Methods

Study Population

From December 2013 to November 2015, a total of 55 patients with ACS undergoing percutaneous coronary intervention (PCI) at Chiba University Hospital (Chiba, Japan) with measurements of both SUA level on admission and RHI were retrospectively enrolled in this study[6]. They were classified into three groups according to the tertiles of SUA level. The present study was conducted according to the Declaration of Helsinki. Written informed consent for examination was obtained from all patients, and the Ethical Committee of Chiba University approved the present study.

Definition

ACS was defined as unstable angina or acute MI developing <48 hours from the onset. The diagnosis of acute MI was according to the third universal definition of myocardial infarction[16]. Unstable angina was diagnosed according to Braunwald's criteria with significant obstructive coronary artery disease[17]. Although the PCI procedures were performed at the operator's discretion in the clinical settings, they were all performed under IVUS guidance. Hypertension, diabetes, and dyslipidemia were defined based on our previous report[6].

Endothelial Function Assessment

Endothelial function was evaluated by RHI using the EndoPAT 2000 device (Itamar Medical Inc., Caesarea, Israel), which has been validated to assess endothelial function with non-invasive, operator-independent, and reproducible procedure[13, 18, 19]. The principle of measuring RHI has been previously described[20, 21]. Briefly, the patients fasted and refrained from caffeine, tobacco, and all types of medications for at least 8 hours. The measurement was performed in a quiet and temperature-controlled room early in the morning. A finger probe was placed on each index finger, and pulsatile volume changes in the distal digit were recorded by the EndoPAT 2000 device. After a 5-min baseline measurement, the cuff of blood pressure on the tested arm was inflated to obtain complete occlusion for 5 min. Then, the cuff was deflated, and the EndoPAT 2000 device continued to trace peripheral arterial tonometry for another 5 min. The data were automatically analyzed for calculation of RHI, which is the ratio of amplitude of the signal after cuff deflation divided by that before cuff inflation, indexed to the contralateral arm. RHI was measured on the day of discharge or a day earlier (5.8±3.0 days after PCI). On the same morning, trained nurses measured blood pressure of the patients lying in the supine position using an automated cuff sphygmomanometer (ES-H55, Terumo, Tokyo, Japan).

Statistical Analysis

Statistical analysis was performed using SAS statistical software package version 9.4 (SAS Institute, Cary, NC). Data are presented as mean±SD or frequency (%). Continuous variables were compared by analysis of variance and categorical variables with Fisher's exact test. The Kolmogorov–Smirnov test was used to examine the normal distribution of continuous variables. Univariate analysis for the variables in **Table 1** was performed using linear regression analysis of rank-transformed outcomes. We included age, sex, and variables with a p-value of <0.20 on univariate analysis to conduct multivariate analysis by multiple linear regression analysis of rank-transformed outcomes. A p-value of <0.05 was considered statistically significant. Because this was a retrospective study, no power calculation was performed.

Results

Mean SUA level on admission and RHI were 5.8 ±1.5 mg/dl and 1.88±0.58, respectively. RHI was normally distributed ($p=0.36$), and there was a significant negative correlation between SUA level and RHI ($r=-0.41$, $p=0.002$). In addition, SUA level was negatively correlated with RHI ($r=-0.36$, $p=0.02$) only in male patients ($n=42$). The tertiles of SUA level were as follows: low tertile, ≤ 5.2 mg/dl; intermediate tertile, 5.3 to 6.5 mg/dl; and high tertile, ≥ 6.6 mg/dl. **Table 1** lists baseline characteristics of the patients. A higher proportion of males was observed in the high tertile group, and the patients in this group had greater body mass index and smaller estimate glomerular filtration rate compared with the other two groups. Additionally, the decrease of RHI was stepwisely observed in favor of the higher tertile groups (2.14±0.74 vs. 1.84±0.45 vs. 1.67±0.38, $p=0.04$; **Fig. 1**). Multivariate analysis showed elevated SUA level as an independent predictor of RHI value (**Table 2**).

Discussion

The present study showed that SUA level was significantly associated with endothelial function assessed by RHI in patients with ACS. ACS with greater coronary plaque burden or lipid-rich components, advancing through endothelial dysfunction, has been recognized as an advanced phase of coronary atherosclerosis, and elevated SUA level is suggested to be

Table 1. Patient Characteristics

Variable	Low ($n=19$)	Intermediate ($n=18$)	High ($n=18$)	p value
Age (years)	69.2 ± 8.7	67.4 ± 10.2	64.1 ± 15.3	0.41
Men	10 (53%)	15 (83%)	17 (94%)	0.007
Body mass index (kg/m^2)	22.6 ± 3.5	24.1 ± 3.8	25.6 ± 3.7	0.049
Hypertension	15 (79%)	12 (67%)	16 (89%)	0.28
Diabetes mellitus	6 (32%)	7 (39%)	4 (22%)	0.57
Dyslipidemia	11 (58%)	15 (83%)	15 (83%)	0.12
Current smoker	4 (21%)	8 (44%)	6 (33%)	0.33
Prior myocardial infarction	2 (11%)	2 (11%)	2 (11%)	>0.99
Clinical presentation				
STEMI	10 (53%)	10 (56%)	9 (50%)	
NSTEMI	5 (26%)	7 (39%)	7 (39%)	0.72
Unstable angina	4 (21%)	1 (6%)	2 (11%)	
eGFR (ml/min/1.73 m^2)	78.9 ± 18.1	72.2 ± 17.1	58.6 ± 18.5	0.004
Serum uric acid (mg/dl)	4.1 ± 0.9	5.8 ± 0.4	7.4 ± 0.6	<0.001
Medical treatment on admission				
ACE-I or ARB	7 (37%)	6 (33%)	12 (67%)	0.09
β blocker	2 (11%)	2 (11%)	6 (33%)	0.13
Calcium channel blocker	6 (32%)	5 (28%)	5 (28%)	0.96
Diuretic	1 (5%)	2 (11%)	2 (11%)	0.78
Statin	5 (26%)	4 (22%)	4 (22%)	0.95
Antihyperuricemic agent	3 (16%)	1 (6%)	5 (28%)	0.20

Patients were divided into 3 groups according to tertiles of SUA level. ACE-I=angiotensin converting enzyme inhibitor; ARB=angiotensin Ⅱ receptor blocker; eGFR=estimate glomerular filtration rate; NSTEMI=non-ST elevation myocardial infarction; STEMI=ST elevation myocardial infarction.
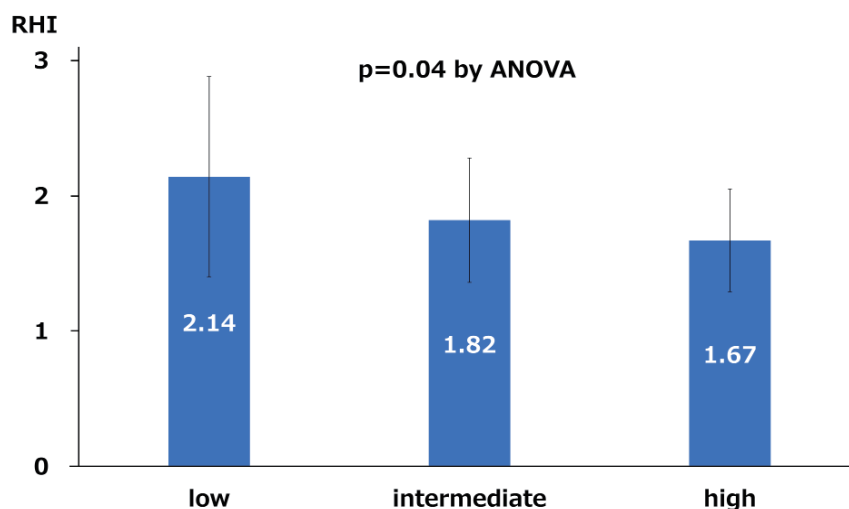

Fig. 1. Relation between RHI and serum uric acid levels divided by the tertiles of SUA level

RHI, reactive hyperemia index

related to the development of atherosclerosis and worse outcomes in patients with ACS. However, their direct relation has not been well studied. To the best of our knowledge, this is the first report investigating the direct relationship between SUA level and endothelial function in such subjects.

The endothelium regulates intravascular homeostasis, vasomotor tone, vascular permeability, inflammation, and smooth muscle cell proliferation and integrates numerous functions, such as blood pressure and coagulation[22, 23]. Endothelial dysfunction progresses the atherosclerotic changes within vascular wall

Table 2. Predictors of reactive hyperemia index

Variable	Univariate		Multivariate	
	r	p value	β	p value
Age (years)	−0.11	0.44	−0.25	0.14
Men	−0.16	0.24	−0.02	0.88
Body mass index (kg/m^2)	−0.06	0.66		
Hypertension	0.03	0.82		
Diabetes mellitus	−0.12	0.38		
Dyslipidemia	0.16	0.25		
Current smoker	−0.08	0.56		
Prior myocardial infarction	0.16	0.25		
STEMI	0.14	0.30		
eGFR (ml/min/1.73m^2)	0.22	0.11	−0.13	0.47
Serum uric acid (mg/dl)	−0.41	0.002	−0.50	0.004
Systolic blood pressure (mm Hg)	−0.13	0.20		
LDL cholesterol (mg/dl)	0.11	0.50		
ACE-I or ARB	0.17	0.23		
β blocker	−0.25	0.07	−0.14	0.29
Calcium channel blocker	−0.06	0.69		
Diuretic	−0.01	0.97		
Statin	0.16	0.23		
Antihyperuricemic agent	−0.09	0.50		

eGFR=estimated glomerular filtration rate; LDL=low-density lipoprotein.

with excessive production of reactive oxygen species and reduction of activity of endothelial nitric oxide synthase[23, 24]. Although SUA has antioxidant capacities[25], it is paradoxically known to have significant associations with inflammation and endothelial dysfunction[9, 26]. Xanthine oxidase (XO), which catalyzes the metabolic reaction of converting purines to uric acid, simultaneously generates reactive oxygen species during the process[23, 27], leading to endothelial dysfunction[28]. In clinical studies, the relation between SUA level and endothelial function has been also well investigated. Kato *et al.* demonstrated that endothelial function assessed by FMD inversely correlated with SUA level in 26 patients without any overt cardiovascular disease ($r=-0.4$, $p=0.05$)[9]. In a series of 263 patients with chronic kidney disease, Kanbay et al. similarly showed that the FMD value was negatively associated with SUA level ($r=-0.49$, $p<0.001$)[12]. The reported correlation coefficients between FMD values and SUA levels in various subjects were considerably varied ranging from −0.73 to −0.26[7, 9, 12, 29-31]. Furthermore, endothelial function can be evaluated using RHI[19, 32] in a non-invasive, reproducible, and operator-independent procedure[13, 18, 19]. To date, there is only one report investigating the association of SUA level with RHI in subjects with metabolic syndrome, which also showed significant correlation between them ($r=-0.21$, $p<0.05$)[33]. In addition to endothe-lial function, the relation of SUA with vascular function was recently reported[34].

Previous studies have demonstrated that elevated SUA level is associated with cardiovascular events in patients with ACS[4, 5]. The retrospective analysis showed higher rates of in-hospital and long-term major adverse cardiovascular events in ST-segment elevation MI patients with high SUA level than in those with low SUA level[5]. Cardiovascular mortality, reinfarction, target vessel revascularization, and severe heart failure were observed more frequently in the high SUA group than in the other groups. Increased cardiovascular mortality and reinfarction in patients with elevated SUA level might be partially explained by our previous report that demonstrated that these subjects had greater lipid content of coronary plaque assessed by IB-IVUS in non-culprit lesion[6]. However, the pathogenesis is partially understood. The present study indicated that the worse outcomes after ACS in patients with elevated SUA level are possibly associated with endothelial dysfunction because RHI has been reported to have prognostic values for cardiovascular events including cardiac death, MI, coronary revascularization, and heart failure[14, 35, 36]. Recently, high XO activity with elevated SUA level in patients with chronic heart failure is reported to lead to cardiac events including cardiac death, ACS, and exacerbation heart failure requiring hospitalization[37]. Thus, ele-

vated SUA level in patients with ACS might induce subsequent poor outcomes by endothelial dysfunction and XO activity. Randomized clinical trial of selective XO inhibitor to investigate whether it reduces adverse events is currently ongoing[38]. Further study is needed to reconfirm the relation and elucidate whether reduction of SUA level or inhibition of XO recover endothelial function and contribute to the improvement of prognosis in patients with ACS.

There are some limitations to the present study. First, this is a single-center study and the number of included patients, especially women, was relatively small. Thus, the result in the present study was hypothesis-generating. Second, endothelial function was assessed by RHI in this study, whereas FMD has been previously used in many studies. Endothelial function assessment with non-invasive procedure has been traditionally and mainly performed by FMD over the recent 2 decades[39]. However, operator dependence limited its use in clinical settings. Although the early report demonstrated a positive correlation between RHI and FMD[40], recent studies did not[32]. Nevertheless, RHI, representing digital microvessel dilation, is considered to assess endothelial function as FMD, which assesses conduit artery vasodilation[32]. RHI and FMD measure distinct components of vascular health, whereas RHI and FMD are reported to predict cardiovascular events with similar prognostic magnitude[19]. Third, patients with ACS may be affected by many factors such as hemodynamic change or recently initiated medication following ACS. However, RHI was measured under the stabilized condition on the day of discharge or a day earlier early in the morning without any medications for at least 8 hours[21]. Lastly, although inflammation reaction and oxidative stress are the key factors in the process of endothelial function, serum inflammation factor (e.g., high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor-α) and oxidative stress marker (e.g., isoprostanes, 8-hydroxy-2' -deoxyguanosine, and thiobarbituric acid reactive substances) were not evaluated in the present study. In conclusion, elevated SUA level was significantly associated with endothelial dysfunction in patients with ACS, possibly leading to subsequent poor outcomes following ACS.

Disclosure

None.

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