Uric acid levels are associated with endothelial dysfunction and severity of coronary atherosclerosis during a first episode of acute coronary syndrome

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Abstract

The role of serum uric acid in coronary artery disease has been extensively investigated. It was suggested that serum uric acid level (SUA) is an independent predictor of endothelial dysfunction and related to coronary artery lesions. However, the relationship between SUA and severity of coronary atherosclerosis evaluated via endothelial dysfunction using peripheral arterial tone (PAT) and the reactive hyperemia index (RHI) has not been investigated during a first episode of acute coronary syndrome (ACS). The aim of our study was to address this point. We prospectively enrolled 80 patients with a first episode of ACS in a single-center observational study. All patients underwent coronary angiography, evaluation of endothelial function via the RHI, and SUA measurement. The severity of the coronary artery lesion was assessed angiographically, and patients were classified in three groups based on the extent of disease and Gensini and SYNTAX scores. Endothelial function was considered abnormal if RHI < 1.67. We identified a linear correlation between SUA and RHI ($R^2 = 0.66$ $P < 0.001$). In multivariable analyses, SUA remained associated with RHI, even after adjustment for traditional cardiovascular risk factors and renal function. SUA was associated with severity of coronary artery disease. SUA is associated with severity of coronary atherosclerosis in patients with asymptomatic hyperuricemia. This inexpensive, readily measured biological parameter may be useful to monitor ACS patients.

Keywords Coronary artery disease · First episode of acute coronary syndrome · Serum uric acid · Endothelial dysfunction

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Introduction

Uric acid is reported to be a mediator of endothelial dysfunction, inflammation, and vascular disease, but its role in coronary artery disease (CAD) remains largely unknown [1]. There is substantial evidence that serum uric acid level (SUA) correlates with many recognized cardiovascular risk factors including age, male sex, hypertension, dyslipidemia, obesity, insulin resistance, hypertension, and diabetes mellitus [1, 2]. Because of these relationships, the association between SUA elevation and cardiovascular disease was considered to be “epiphenomenal” and not causal [3]. However, recent evidence would support the concept that hyperuricemia may be a significant and independent risk factor for cardiovascular disease, especially in ischemic heart disease.

The underlying pathophysiology remains poorly understood. One mechanism has been claimed to explain the dangerous effects of high SUA: endothelial dysfunction [4].

Although high SUA is associated with endothelial dysfunction, a process that has a pivotal role in the promotion of atherosclerosis in healthy subjects [5], no study examined the relationship between SUA, endothelial dysfunction (evaluated using reactive hyperemia index) and coronary artery disease in patients with a first episode of acute coronary syndrome (ACS).

We tested here the hypothesis that SUA is an independent predictor of coronary artery lesions associated with endothelial dysfunction in patients with a first episode of non-ST segment elevation ACS.

Methods

Study population

We performed a single-center, prospective, observational study in 80 patients with a first episode of non-ST segment elevation ACS. Overall, the panel has been previously described [6]. All of the patients underwent coronary angiography, evaluation of endothelial function, and SUA measurement. Exclusion criteria (reported in [6]) were New-York Heart Association functional class II through IV, cardiac arrest, contraindications to antiplatelet therapy, treatment with angiotensin-converting enzyme inhibitors or diuretics—which are known to influence uremia and endothelial function and could therefore be confounders—treatment with a P2Y₁₂-adenosine diphosphate receptor antagonist for < 1 month, platelet count < 100 G/L, history of bleeding diathesis, history of hemorrhagic stroke, stroke in the preceding year, and surgery in the preceding month. The study was approved by the hospital's institutional review board and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Evaluation of endothelial function

All patients underwent evaluation of endothelial function using reactive hyperemia (RH) with non-invasive peripheral arterial tonometry (PAT) [7] on the day after admission. All vasoactive medications were discontinued at least 24 h prior to testing. Microvascular dysfunction (MiD) was evaluated by PAT as reactive hyperemia index (RHI), a measure of endothelial function, and was assessed using the EndoPAT 2000 device (Itamar Medical, Israel). Briefly, a PAT finger probe was placed on each index finger. Pulsatile volume changes of the distal digit induced pressure alterations in the finger cuff that were sensed by a pressure transducer and transmitted to and recorded by the EndoPAT 2000 device. Blood pressure and heart rate were measured by an automated blood pressure monitor. Endothelial function was assessed via the RH-PAT index. Both measures were calculated using a computerized

automated algorithm (software version 3.1.2) provided with the device. Measurements were performed according to the manufacturer's instructions. Briefly, the subjects were in the supine position in a quiet, temperature-controlled (21–24 °C) room with dimmed lights for a minimum of 20 min before the measurement was taken. They were asked to remain as still as possible and silent during the measurement period. Each recording consisted of 5 min of baseline measurement, 5 min of occlusion measurement, and 5 min of post-occlusion measurement (hyperemic period). Occlusion of the brachial artery was performed on the non-dominant upper arm. The occlusion pressure was ≥ 60 mmHg above the systolic blood pressure (minimally 200 mmHg and maximally 300 mmHg). We performed PAT within a short, fixed time-frame of 2 h maximum, between 9:00 and 11:00 a.m., with the patient in a fasted condition and in complete rest, thereby reducing the influence of confounding factors such as circadian variability. Patients were advised to continue their current medication and lifestyle for the duration of the study. The ratio of the PAT signal after cuff release compared with baseline was calculated through a computer algorithm that automatically normalized for baseline signal and was indexed to the contralateral arm. The estimated ratio reflects the RHI. RHI values < 1.67 were considered abnormal. The patients were not allowed any caffeine-containing drinks, to undertake strenuous exercise, or to consume tobacco for at least 12 h before the examination.

Angiography findings

Because presence of coronary plaques and morphological findings using coronary angiography reportedly improve the prediction of cardiovascular events, two different interventional cardiologists independently reviewed the angiographic films. The complexity and extent of the coronary lesions were assessed angiographically. The lesions were analyzed in multiple projections, and reference vessel diameter, minimal lumen diameter, and percent diameter stenosis were measured from the “worst” angiographic view. Significant angiographic narrowing was defined as > 50% diameter stenosis involving either one major epicardial vessel at any site or any collateral with > 3 mm diameter.

The extent of CAD was defined as the number of diseased coronary arteries. Patients were classified as having one-, two-, or three-vessel disease if they had a single lesion in one, two, or three or more coronary vessels, respectively. Lesions on each major epicardial vessel plus a lesion on a large diagonal branch was classified as three-vessel disease. Multiple lesions of the same vessel separated by > 20 mm of normal artery segment were classified as two-vessel disease.

Severity of disease was determined according to the Gensini score [8]. The population was divided into three groups: low score (< 20), intermediate score (21–60), and high score (> 61).

Synergy Between PCI with Taxus and Cardiac Surgery Score (SYNTAX) is an angiographic scoring system used to evaluate the complexity of coronary atherosclerosis and anatomy [9]. SYNTAX score is reportedly an effective tool for predicting a major cardiovascular event risk in stable patients with multivessel or left main CAD and in patients with ACS [9]. In this study, patients were divided into tertiles based on SYNTAX scores: low (≤ 18), intermediate (> 18 –27), and high (> 27).

Laboratory measurements

Blood sampling was performed in the morning, after 12 h of fasting. Samples of venous blood (6–8 mL) were collected from each subject between 08:00 a.m. and 09:00 a.m., after an overnight fast. Blood samples were collected before the angiography, and hematological and biochemical profiles were measured. SUA was measured using the Cobas 8000 apparatus (Roche®, Swiss). According to a previous study, hyperuricemia was defined as a SUA > 420 $\mu\text{mol/L}$ in men and 360 $\mu\text{mol/L}$ in women [10].

Statistical analysis

Data are expressed as counts and percentages or means with standard deviations. A scatter plot was designed to explain the relationship between the two continuous variables (SUA levels and RHI) and boxplots for the relationship between the continuous variable (RHI) and the categorical ordinal variables (CAD extent: number of disease vessels; CAD severity: Gensini score; CAD complexity: SYNTAX score).

For univariate analyses, associations between RHI and discriminant variables were evaluated: continuous variables (age, body mass index, and SUA) were analyzed using Spearman's correlation tests. Mean-based comparisons of the RHI between various subgroups (sex, smoking, diabetes mellitus, hypertension, estimated glomerular filtration rate, and family history of CAD) were calculated using non-parametric Mann–Whitney tests. Multiple linear regression analysis was performed to confirm the link between SUA and RHI with adjustment for covariates. The variables relevant to the models were risk factors for endothelial dysfunction (including estimated glomerular filtration rate) and variables selected from the univariate analyses based on a threshold P value ≤ 0.20 (SUA, age, sex, body mass index, smoking, diabetes mellitus, hypertension, family history of CAD and dyslipidemia).

The final model incorporated the standardized beta coefficients, which represent a change in the standard deviation of the dependent variable (RHI) resulting from a change of one standard deviation in the various independent variables. The independent variables with the higher standardized beta coefficients are those with a greater relative effect on RHI levels.

All the tests were two-sided and statistical significance was set at $P \leq 0.05$. The statistical analyses were performed using

the SPSS version 20.0 software package (SPSS Inc., Chicago, IL, USA). Investigators were blinded to SUA and RHI data at the time of inclusion.

Results

Patient clinical and laboratory data are given in Table 1. The mean age of the population was 67.8 ± 9.4 years, 61.3% were men, and one third had three risk factors. The mean SUA was 490.8 ± 94.5 $\mu\text{mol/L}$. Most of the admissions were for NSTEMI (60.0%) and for one-vessel (53.8%) or two-vessel (33.8%) CAD. There was no difference between men and women regarding SUA (56.9% of men and 43.1% of women had asymptomatic hyperuricemia). Normal renal filtration (> 90 mL/min/1.73 m²) was present in 76.3% and moderate dysfunction in 23.8%. Moderately impaired renal function was not associated with high SUA. A high score for CAD extent was present in 12.5% of the population; 16.3% had a high Gensini score, and 10.0% a high SYNTAX score. Moderately impaired renal function was not correlated with extent, severity, or complexity of CAD.

Endothelial dysfunction and uricemia

All patients exhibited endothelial dysfunction (mean RHI 1.4 ± 0.1 ; normal value > 1.67). In univariate analyses, RHI was associated with SUA, age, sex, body mass index, smoking, diabetes mellitus, dyslipidemia, and hypertension (all $P < 0.001$; Table 2). In the multivariate analysis, the relationship between SUA and RHI remained significant, even after adjusting for other covariates or confounders ($\beta = -0.72$, $p = < 0.001$). SUA was the strongest predictor of endothelial dysfunction. The associations between body mass index and hypertension with RHI were also significant ($\beta = -0.17$, $p = 0.012$ and $\beta = -0.17$, $p = 0.026$, respectively) (Table 3). There was a negative linear correlation between SUA and endothelial dysfunction in patients with asymptomatic hyperuricemia (Fig. 1; $R^2 = -0.66$; $P < 0.001$).

Uricemia and angiographic findings

The inter-observer correlation coefficient of the different scores was 0.96 for the interpretation of angiograms, and the intra-observer variability was 0.98. Tertiles (low, intermediate, high) of the distribution of CAD extent, Gensini score, and SYNTAX score according to SUA are presented in Figs. 2, 3, and 4, respectively. SUA was associated with the extent of CAD in men and women. SUA was associated with Gensini and SYNTAX scores based on multivariable linear regression analysis (Supplementary Table), with high SUA, extent of

Table 1 Characteristics of study population

Variable	<i>n</i> = 80
Demographics	
Age in years, mean ± SD	67.8 ± 9.4
Male sex, <i>n</i> (%)	49 (61.3)
Body mass index in kg/m ² , mean ± SD	26.8 ± 2.9
Traditional cardiovascular risk factors, <i>n</i> (%)	
Smoking	27 (33.8)
Hypercholesterolemia	15 (18.8)
Diabetes mellitus	23 (28.8)
Hypertension	27 (33.8)
Family history of CAD	7 (8.8)
Acute coronary syndrome diagnosis, <i>n</i> (%)	
NSTEMI	48 (60.0)
Unstable angina	32 (40.0)
Angiography and intervention, <i>n</i> (%)	
CAD extent: number of diseased vessels, <i>n</i> (%)	
1	43 (53.8)
2	27 (33.8)
3	10 (12.5)
CAD severity: Gensini score, mean ± SD	37 ± 22.5
< 20, <i>n</i> (%)	25 (31.3)
20–60, <i>n</i> (%)	42 (52.5)
> 60, <i>n</i> (%)	13 (16.3)
CAD complexity: SYNTAX score, mean ± SD	21.3 ± 8.8
< 23, <i>n</i> (%)	46 (57.5)
23–33, <i>n</i> (%)	26 (32.5)
> 33, <i>n</i> (%)	8 (10.0)
Evaluation of endothelial function	
RHI, mean ± SD	1.4 ± 0.1
eGFR in mL/min/1.73 m ² , mean ± SD	98.8 ± 9.1
> 90, <i>n</i> (%)	61 (76.3)
60–90, <i>n</i> (%)	19 (23.8)
Laboratory data	
Serum uric acid in μmol/L, mean ± SD	490.8 ± 94.5
Asymptomatic hyperuricemia, <i>n</i> (%)	
> 420 μmol/L in men	37 (56.9)
> 360 μmol/L in women	28 (43.1)

CAD coronary artery disease, eGFR estimated glomerular filtration rate, NSTEMI non-ST-segment elevation myocardial infarction, RHI reactive hyperemia index, SD standard deviation

CAD, and severity and complexity scores indicating more severe coronary atherosclerosis.

Discussion

Our study suggests that a significant and independent relationship exists between SUA and endothelium dysfunction in patients with a first episode of ACS. Furthermore, SUA is

Table 2 Factors associated with RHI on univariate analysis

Factor	RHI (mean ± SD) or R	<i>P</i> value
Serum uric acid	− 0.82	< 0.001
Age	− 0.59	< 0.001
Women	1.44 ± 0.09	
Men (ref)	1.34 ± 0.13	< 0.001
Body mass index	− 0.37	< 0.001
Smoking	1.31 ± 0.13	< 0.001
No (ref)	1.42 ± 0.11	
Diabetes mellitus	1.26 ± 0.09	< 0.001
No (ref)	1.43 ± 0.11	
Hypertension	1.26 ± 0.06	< 0.001
No (ref)	1.42 ± 0.12	
eGFR > 90 mL/min/1.73 m ²	1.39 ± 0.12	0.33
60–90 mL/min/1.73 m ² (ref)	1.35 ± 0.14	
Family history of CAD	1.45 ± 0.07	0.09
No (ref)	1.37 ± 0.13	
Dyslipidemia	1.28 ± 0.12	< 0.001
No (ref)	1.40 ± 0.12	

CAD coronary artery disease, *R* Spearman's correlation coefficient, *ref* reference; RHI reactive hyperemia index; SD standard deviation

positively associated with the extent, severity, and complexity of CAD.

Uricemia and endothelium dysfunction

It is well established that purines are involved in vascular tone and endothelium function [11]. Erdogan et al. [5] demonstrated that in healthy subjects, increased SUA, even in the physiological range, reduced brachial artery flow-mediated dilation independently of other cardiovascular risk factors. Zoccali et al. [12] demonstrated an inverse relationship between SUA and endothelial dysfunction assessed by acetylcholine-stimulated vasodilation in 217 patients with uncomplicated, untreated essential hypertension, independently of traditional cardiovascular risk factors. Kato et al. [13] reported that impaired endothelial-dependent vasodilation is present in hyperuricemic patients even in the absence of symptomatic cardiovascular disease. Recently, Canepa et al. [14] showed an association between SUA and arterial stiffness in men. Two placebo-controlled studies demonstrated a direct relationship between the allopurinol-induced reduction of SUA and improvement in endothelial function [15, 16]. However, these studies used different methods for assessing endothelial function (high-precision ultrasound) and were based on relatively small numbers of subjects. Recently, Li et al. [17] confirmed the findings from animal studies [18–20], that high SUA triggers endothelial dysfunction, inducing apoptosis and reducing endothelial nitric oxide

Table 3 Factors associated with RHI, multivariable analysis ($R^2 = 0.76$) in 80 ACS patients

	RHI (mean $\pm$ SD) or R	β	P value
Serum uric acid	− 0.82	− 0.72	< 0.001
Age	− 0.59	0.04	0.67
Women	1.44 $\pm$ 0.09	0.02	0.73
Men (ref)	1.34 $\pm$ 0.13		
Body mass index	− 0.37	− 0.17	0.012
Smoking	1.31 $\pm$ 0.13	− 0.08	0.30
No (ref)	1.42 $\pm$ 0.11		
Diabetes mellitus	1.26 $\pm$ 0.09	− 0.04	0.61
No (ref)	1.43 $\pm$ 0.11		
Hypertension	1.26 $\pm$ 0.06	− 0.17	0.026
No (ref)	1.42 $\pm$ 0.12		
eGFR > 90 mL/min/1.73 m ²	1.39 $\pm$ 0.12	− 0.08	0.22
60–90 (ref)	1.35 $\pm$ 0.14		
Family history of CAD	1.45 $\pm$ 0.07	0.05	0.44
No (ref)	1.37 $\pm$ 0.13		
Dyslipidemia	1.28 $\pm$ 0.12	− 0.02	0.75
No (ref)	1.40 $\pm$ 0.12		

β indicates the standardized β -coefficient (where β represents the change in the SD in RHI levels resulting from a change of one SD in the independent variable), CAD coronary artery disease, eGFR estimated glomerular filtration rate, R Spearman's correlation coefficient, ref reference, RHI reactive hyperemia index, SD standard deviation

synthase activity and nitric oxide production. These studies showed that elevated SUA causes endothelial dysfunction, leading to reduce nitric oxide levels that have a pivotal role in the promotion of atherosclerosis and genesis of acute vascular events. However, these studies were performed in vitro, in animals, or in healthy populations monitored using various endothelial dysfunction tests that lack specificity. In the present study involving patients with a first episode of ACS, we

used PAT that is less operator-dependent [6, 21]. Furthermore, our population was homogeneous (CAD patients with a first episode of non-ST segment elevation ACS) and statistical analysis took into account the factors that may interfere with the metabolism of acid uric, e.g., impaired renal function, sex, and cardiac risk factors.

In our study, we observed a negative correlation between SUA and RHI irrespective of SUA. Recent data do not support

Fig. 1 Scatter plot showing linear relationship between serum uric acid level (SUA) and reactive hyperemia index (RHI). Solid black line indicates median, box indicates interquartile range, and upper and lower whiskers indicate range. Linear R^2 : coefficient of determination

Fig. 2 Boxplot showing repartition of SUA in terms of extent of CAD (number of diseased vessels). Solid black line indicates median, box indicates interquartile range, and upper and lower whiskers indicate range

the hypothesis of a causal relationship between uric acid and endothelial dysfunction. In a randomized, double-blind, placebo-controlled trial in overweight or obese individuals, a pharmacological reduction of SUA using probenecid or allopurinol did not affect endothelial function monitored by brachial artery ultrasound [22]. These findings suggest that SUA could be a marker rather than a player in the pathogenesis of cardiovascular disease.

Uricemia and coronary artery disease

In the present study with CAD patients, mean SUA was high, and most of the patients presented with asymptomatic hyperuricemia (56.9% in men and 43.1% in women) as previously described (see Table 1) [23, 24]. Hyperuricemia was defined as SUA > 420 μmol/L in men and > 360 μmol/L in women, whereas in most studies, hyperuricemia was defined as

Fig. 3 Boxplot showing repartition of SUA in terms of severity of CAD (Gensini score). Solid black line indicates median, box indicates interquartile range, and upper and lower whiskers indicate range

Fig. 4 Boxplot showing repartition of SUA in terms of complexity of CAD (SYNTAX score). Solid black line indicates median, box indicates interquartile range, and upper and lower whiskers indicate range

SUA > 420 μM irrespective of sex. Recently, Fromonot et al. [25] reported that patients with established CAD have increased SUA compared with healthy individuals. They also found that SUA was higher in ACS vs stable CAD. Furthermore, they found a correlation between SUA, adenosine, and homocysteine level. Thus, high SUA may result from an increase in adenosine plasma level that occurs during severe CAD [26, 27] and/or from an increase in homocysteine, another well-known risk marker of CAD [29]. Interestingly, A_{2A} adenosine receptors that control the coronary blood flow are downregulated in CAD patients [28, 29].

The fact that our study concerned ACS, with most patients diagnosed with NSTEMI and untreated with xanthine oxidase inhibitors, may explain the high SUA. Regarding the relationship between SUA and severe coronary atherosclerosis, several retrospective or prospective studies reported significant correlations. Sinan Deveci et al. [30] using the Gensini score found an association of severity of ischemic heart disease with SUA. Conversely, Gur et al. [31] concluded that SUA is associated with the presence but not the severity of CAD. In ACS, Duran et al. [32] reported an association of hyperuricemia with angiographic severity of ischemic heart disease (measured using the Gensini score). Barbieri et al. [33] showed that SUA was significantly higher in men, while high SUA was associated with severe CAD in women only. Zhang et al. [34] demonstrated that SUA is markedly related to the prevalence of CAD and development of multivessel disease in premenopausal women and is an independent risk factor for CAD in this group. In Chinese patients, SUA was independently associated with the severity of CAD in patients with obstructive CAD assessed by SYNTAX score [35]. Many of the studies suggest that SUA is associated with an increased risk of CAD, but meta-analyses have not reached agreement

as to the utility of uric acid as a cardiovascular risk factor [36, 37]. However, the criteria used (e.g., for hyperuricemia and for angiographic findings) and the variables controlled for in the adjustment (e.g., use of antihypertensive or cholesterol-lowering drugs or diuretics) were not homogeneous. Moreover, previous treatment with xanthine oxidase inhibitors was not considered. In the present study, patients were with a first episode of ACS, normal (or moderately impaired) estimated glomerular filtration rate, and without confounding treatments. Using this panel, we found that SUA is associated with the extent, severity, and complexity of CAD independently of traditional risk factors and may be a surrogate marker of atherosclerosis [8, 9]. Because uric acid is the final product of purine metabolism, the players of CAD may be molecules participating upstream in the purine pathway. This last point needs further investigations.

Study limitations

Although this is the first report on the association between endothelial damage, established CAD, and SUA in ACS patients, important limitations must be considered: this was a single-center observational study with a limited number of patients and no control cohort.

Conclusion

SUA appears to be associated with increased risk for endothelium dysfunction, CAD severity, and complexity in ACS. These results suggest that monitoring of SUA, an inexpensive

and easily measurable biomarker, provides information on risk stratification in patients with a first episode of ACS.

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Compliance with ethical standards

Conflicts of interest Mélanie Gaubert declares that she has no conflict of interest.

Marion Marlinge declares that she has no conflict of interest.

Marine Alessandrini declares that she has no conflict of interest.

Marc Laine declares that he has no conflict of interest.

Laurent Bonello declares that he has no conflict of interest.

Julien Fromonot declares that he has no conflict of interest.

Jennifer Cautela declares that she has no conflict of interest.

Franck Thuny declares that he has no conflict of interest.

Jeremie Barraud declares that he has no conflict of interest.

Giovanna Mottola declares that he has no conflict of interest.

Pascal Rossi declares that he has no conflict of interest.

Emmanuel Fenouillet declares that he has no conflict of interest.

Jean Ruf declares that he has no conflict of interest.

Régis Guieu declares that he has no conflict of interest.

Ethical approval The study was approved by the hospital's institutional review board and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

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