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Uric Acid Is Associated with Worsening of Diastolic Function and Adverse Outcomes in Patients with Coronary Slow Flow

Ürik Asitin Koroner Yavaş Akımlı Hastalarda Diyastolik Fonksiyonunun Kötüleşmesi ve Advers Sonuçlarla İlişkisi

ABSTRACT

Objective: The impact of uric acid on worsening of diastolic function and clinical outcomes in patients with coronary slow flow remains unclear. This study aims to investigate possible associations between serum uric acid, worsening of diastolic function, and major adverse cardiovascular events in coronary slow flow patients.

Methods: Blood samples were obtained prospectively from 537 patients who had been angiographically diagnosed with coronary slow flow. Of those, 425 patients underwent comprehensive cardiac function assessment both before and after maximal treadmill exertion by stress echocardiography. The association between serum uric acid and major adverse cardiovascular events was examined using Cox proportional hazards regression model.

Results: Among the 425 patients (mean age: 58 ± 11 years; 52.2% men), worsening of diastolic function occurred in 176 (41.4%) after exercise stress. Patients with worsening of diastolic function had elevated levels of serum uric acid compared to those without (5.7 [4.1, 6.7] vs 4.3 [3.6, 5.3] mg/dL, respectively; $P < .001$). Higher serum uric acid levels were also significantly associated with neutrophil counts and high-sensitive C-reactive protein in patients with worsening of diastolic function but not in those without. Multivariate regression analysis found serum uric acid to be an independent predictor of worsening of diastolic function (odds ratio = 1.87 [1.17-3.82], $P = .023$). Moreover, serum uric acid remained associated with major adverse cardiovascular events even after adjusting for echocardiographic and clinical variables (hazard ratio = 1.56 [1.03-2.89], $P = .016$).

Conclusion: Serum uric acid is associated with worsening of diastolic function and may be mediated by inflammation. These findings indicate that uric acid is a risk factor for major adverse cardiovascular events in patients with coronary slow flow.

Keywords: Coronary slow flow, major adverse cardiovascular events, uric acid, worsening of diastolic function

ÖZET

Amaç: Koroner yavaş akımlı hastalarda ürik asidin diyastolik fonksiyonun kötüleşmesi ve klinik sonuçlar üzerindeki etkisi belirsizliğini korumaktadır. Bu çalışma, koroner yavaş akım hastalarında serum ürik asit, diyastolik fonksiyonun kötüleşmesi ve majör advers kardiyovasküler olaylar arasındaki olası ilişkileri araştırmayı amaçlamaktadır.

Yöntemler: Anjiyografik olarak koroner yavaş akım tanısı konulan 537 hastadan prospektif olarak kan örnekleri alındı. Bunlardan 425 hastaya stres ekokardiyografi ile maksimum koşu bandı eforunun hem öncesinde hem de sonrasında kapsamlı kardiyak fonksiyon değerlendirmesi yapıldı. Serum ürik asit ile majör advers kardiyovasküler olaylar arasındaki ilişki, Cox orantılı tehlikeler regresyon modeli kullanılarak incelendi.

Bulgular: 425 hastadan (ortalama yaş: 58 ± 11 yıl; %52,2 erkek) 176'sında (%41,4) egzersiz stresinden sonra diyastolik fonksiyonda kötüleşme meydana geldi. Diyastolik fonksiyonu kötüleşen hastalarda, diğerlerine kıyasla serum ürik asit seviyeleri yüksekti (sırasıyla 5,7 [4.1, 6.7] ve 4.3 [3.6, 5.3] mg/dL; $P < .001$). Yüksek serum ürik asit seviyeleri, diyastolik fonksiyonu kötüleşen hastalarda nötrofil sayıları ve yüksek duyarlı C-reaktif protein ile de anlamlı şekilde ilişkiliydi, ancak yüksek olmayanlarda böyle bir ilişki yoktu. Çok değişkenli regresyon analizi, serum ürik asidin diyastolik fonksiyonun kötüleşmesinin bağımsız bir öngörücüsü olduğunu ortaya koydu (odds oranı = 1.87 [1.17-3.82], $P = .023$). Ayrıca, serum ürik asit, ekokardiyografik ve klinik değişkenler için düzeltme yapıldıktan sonra bile majör advers kardiyovasküler olaylarla ilişkili bulundu (risk oranı = 1.56 [1.03-2.89], $P = .016$).

ORIGINAL ARTICLE
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Sonuç: Serum ürik asit, diyastolik fonksiyonun kötüleşmesi ile ilişkilidir ve inflamasyon aracılık edebilir. Bu bulgular, ürik asidin koroner yavaş akımı olan hastalarda majör advers kardiyovasküler olaylar için bir risk faktörü olduğunu göstermektedir.

Anahtar Kelimeler: Koroner yavaş akım, ürik asit, diyastolik fonksiyonun kötüleşmesi, majör advers kardiyovasküler olaylar

Delayed distal vessel opacification that occurs without obstructive coronary artery disease is referred to as coronary slow flow (CSF).[1] Previous studies have shown that chest pain, electrocardiographic changes, and other complications such as arrhythmias or sudden cardiac death were more common in CSF patients.[2,3] The incidence of CSF in patients with suspected cardiovascular disease who undergo coronary angiography has been estimated at up to 7%.[4] Some studies indicate that left ventricular (LV) systolic and diastolic functions are preserved in CSF patients.[3] However, CSF may impair exercise capacity and most patients who present as emergency cases with CSF are admitted to hospital for recurrent chest pain or myocardial infarction.[5] Furthermore, abnormal LV diastolic function is often the first sign of LV dysfunction caused by a variety of diseases, including coronary artery disease, hypertension, and diabetes mellitus.[6,7] Worsening of diastolic function (WDF) during exercise stress may be a marker of myocardial ischemia and thus related to adverse outcomes in CSF patients.[8]

An elevated level of serum uric acid (SUA) is known to independently predict cardiovascular events.[9,10] In addition, recent studies have shown the SUA level is significantly associated with coronary blood flow and that high levels of SUA could independently predict CSF. The underlying mechanism for the link between uric acid and cardiovascular events in CSF patients is still unclear.[11,12] Preliminary data suggest that the effects of SUA in CSF may be a consequence of increased inflammation and oxidative stress in the vascular endothelium, resulting in impaired nitric oxide synthesis leading to endothelial dysfunction. However, the data on possible associations between SUA, inflammation, and WDF are limited.[10,13] To develop more effective and preventive strategies, the aim of this study was to investigate the relationship between SUA, inflammation, and WDF in CSF patients and to determine the predictors of major adverse cardiovascular events (MACE) in this population.

Methods

The study cohort was composed of patients referred to the Center of Cardiology of First Affiliated Hospital of Tsinghua University and the Department of Cardiology of Beijing Anzhen Hospital for cardiac catheterization with angiographically diagnosed CSF from January 2016 to December 2020. The blood tests conducted for all cases included the measurement of high-sensitive C-reactive protein (hs-CRP), complete blood count with differential, SUA, and a basic chemistry panel. The study excluded patients with a history of congestive heart failure, coronary artery disease (including plaque, spasm, or ectasia), valvular heart disease, peripheral vascular disease, chronic systemic disease, fever or active infection, chronic kidney disease, chronic obstructive pulmonary disease, and with known gout disease and also excluded patients requiring dobutamine stress echocardiography, those with resting left bundle branch block, and those with a paced rhythm or atrial fibrillation. Worsening of diastolic function was defined as a >25% increase in E/e' (stress-rest) as assessed by stress echocardiography (SE).[8] Patients were divided into those with WDF and without WDF. Medications that affect heart rate such as metoprolol tartrate were discontinued for 48 hours prior to stress echocardiography. Ethics Committees of Tsinghua University and Capital Medical University gave approval for this study, and written informed consent was obtained from the patients. This study was performed in accordance with the Declaration of Helsinki.

Measurement of Thrombolysis in Myocardial Infarction (TIMI) Frame Count and Definition of Coronary Slow Flow

Coronary angiography was performed via radial artery access using the standard Judkins technique. The patients were assessed for the presence of CSF during coronary angiography. Coronary flow rates were quantified by using the TIMI frame count (TFC) method in multiple angulated views. The number of cine frames from the introduction of dye in the coronary artery to a predetermined distal landmark was counted. Distal landmarks were determined as follows: the distal bifurcation for left anterior descending (LAD), left circumflex (LCX), and the first branch of the posterolateral artery for right coronary artery (RCA). Since LAD is longer than the other major coronary arteries, TFC for LAD was corrected by dividing it by 1.7. Study participants with a TFC greater than 2 standard deviations (SD) from the published normal range for any 1 of the 3 vessels (>40.6 frames for LAD, >29.8 frames for LCX, and >27.3 frames for RCA) were accepted as having CSF. Two observers blinded to the clinical details of the individual participants independently quantified the coronary flow using TFC. The diagnosis of CSF was based on the criteria proposed by Gibson et al.[14]

Resting and Stress Echocardiography

Exercise was induced using medical-grade treadmills and Case Systems (Milwaukee, USA). Exercise stress was generated in a controlled and reproducible setting using standard Bruce protocols.[15] Patients were exercised until their heart rate (HR) reached at least 85% of the predicted maximum for their age or if they developed limiting symptoms.[16] Echocardiographic

ABBREVIATIONS

CSF	Coronary slow flow
HR	Heart rate
hs-CRP	High sensitive C-reactive protein
LAD	Left anterior descending
LAVi	Left atrial volume index
LCX	Left circumflex
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
RCA	Right coronary artery
SE	Stress echocardiography
SUA	Serum uric acid
TFC	TIMI frame count
WDF	Worsening of diastolic function

images were acquired using Vivid E9 Vingmed Ultrasound (GE, Horten, Norway) during rest in the parasternal long-axis, short-axis, and apical 4, 2, and 3 chambers. For optimal efficacy, stress images were obtained immediately (60-90 seconds) after the peak stress. Left ventricular ejection fraction (LVEF) was measured using Simpson's method. A standardized method was used to evaluate the diastolic function as per the most recent guidelines published by the European Association of Cardiovascular Imaging.[17] This uses a combination of echocardiographic variables including the pulmonary venous flow pattern, the transmitral inflow pattern, and mitral annular velocities with tissue Doppler imaging.

The left atrial volume was measured in apical 4- and 2-chamber views and then averaged using the disk method.[6] The mitral inflow pulsed-wave Doppler, including E-wave and A-wave velocities, were measured and compared to the pulsed-wave tissue Doppler imaging e' wave velocity at the medial and lateral mitral annulus, as per guidelines, in the apical 4-chamber view. The mitral E/e' ratio was then averaged. All tests were performed under supervision, and the images were read in a blinded manner by a cardiologist specialized in SE and by an exercise physiologist. The images were subsequently reread, standardized, and then recorded by a SE-specialized cardiologist who was blinded to the results and outcomes.

Clinical Data

The clinical data recorded were patient age, gender, body mass index, comorbidities, and medications. In addition, resting and peak stress HR and blood pressure were recorded prospectively. The definition of hypertension used in this study was blood pressure > 140/90 mmHg or a history of hypertension with current anti-hypertensive medications. The definition of diabetes mellitus was fasting blood glucose >126 mg/dL on 2 occasions, or treatment using anti-diabetic agents. Major adverse cardiovascular event for this study was defined as stroke, myocardial infarction, rehospitalization, or cardiac death during the median follow-up of 1.8 years (interquartile range, 0.6-3.2 years). Cardiac death was defined as sudden death with no other explanation available and death due to arrhythmia or after myocardial infarction or heart failure. All clinical events were adjudicated by an independent Clinical Endpoints Committee.

Reproducibility

Intra- and interobserver reproducibility was assessed by calculating the difference between the values of 20 randomly selected patients measured by one observer twice and by a second observer.

Statistical Analysis

Continuous variables were expressed as the mean ± SD or medians and quartiles. These were compared using the Student *t*-test or Mann–Whitney *U* test. Categorical variables were expressed as numbers and percentages and compared with chi-square or Fisher's exact tests. Inter-group differences were analyzed using the paired *t*-test. Possible predictors of WDF were determined by univariate logistic regression, and variables that were statistically significant ($P < .05$) were selected for evaluation by the multivariate logistic regression model. The association of SUA with MACE was examined with a Cox proportional hazards model. Univariate analysis was first used to identify the factors with a significance level of $P < .05$ to include in the model. Inter- and intraobserver reproducibility of LVEF, LAVi, E-wave, A-wave, and e' wave was assessed using intra-class correlation coefficients (ICCs) and Bland–Altman analysis. Data were analyzed using Statistical Package for the Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA). A two-tailed $P < .05$ was considered statistically significant.

Results

Study Population

Among the 537 patients identified with CSF, 425 who had undergone comprehensive cardiac function assessment before and after exercise stress were included in this study. Type 2 diabetes mellitus was present in 7.8% of patients, hypertension in 42.6%, and hyperlipidemia in 40.2%. The mean SUA level was 4.8 ± 1.6 mg/dL. The mean age of the overall study population was 58 ± 11 years and 52.2% were male.

Baseline Clinical Characteristics

The clinical characteristics of this study cohort are shown in Table 1. Overall, 176 (41.4%) patients had WDF and 249 (58.6%) did not. Patients with WDF showed significantly higher levers of SUA, neutrophil counts, hs-CRP, triglycerides, E/e'_{post} and more prevalence of hyperlipidemia, and alcohol consumption compared to those without WDF. In addition, patients with WDF were prescribed febuxostat and lipid-lowering medications at significantly higher frequencies. However, there were no significant differences in age, gender, body mass index, the prevalence of diabetes mellitus and hypertension, total cholesterol, LDL-c, HDL-c, smoking history, LVEF, LAVi, or E/e'_{pre} between patients with or without WDF.

Correlations of Serum Uric Acid with Percent Change (Stress-Rest) in E/e' and Inflammatory Markers

A significant association was found between SUA and the percentage change (stress-rest) in E/e' ($P = .002$; Figure 1). In patients with WDF, linear regression modeling showed that higher SUA levels correlated significantly with neutrophil counts ($P = .005$; Figure 2) and with higher levels of hs-CRP ($P = .009$; Figure 3). However, the SUA level failed to correlate with inflammatory markers in patients without WDF ($P = .132$).

Predictors of worsening of Diastolic Function

Analysis using univariate logistic regression found that hyperlipidemia (OR = 1.59 [1.13-3.46], $P = .014$), alcohol consumption (OR = 1.47 [1.06-3.68], $P = .021$), triglycerides (OR = 1.71 [1.09-2.43], $P = .011$), neutrophil counts (OR = 1.58 [1.04-3.08], $P = .012$), hs-CRP (OR = 1.73 [1.13-3.94], $P = .007$), SUA (OR = 2.87 [1.56-5.38], $P < .001$), febuxostat use (OR = 0.88 [0.56-0.93], $P = .010$) showed significant association with WDF. However, SUA remained significantly associated with WDF (OR = 1.87 [1.17-3.82], $P = .023$) in multivariate logistic regression analysis (Table 2).

Clinical Outcomes

During a median follow-up of 1.8 years (interquartile range, 0.6-3.2 years), 93 patients developed MACE. Of these, 69 (39.2%) occurred in patients with WDF and 24 (9.6%) in those without WDF. The level of baseline uric acid in patients who developed MACE was higher than in those who failed to develop MACE (interquartile range, 5.7 [4.8-6.7] vs 4.6 [3.8-5.3]; $P < .001$;

Table 1. Baseline Clinical Characteristics Based on the Worsening of Diastolic Function

Variable	Patients With WDF (n=176)	Patients Without WDF (n=249)	*P*
Age (years)	55 (IQR, 51-65)	54 (IQR, 50-63)	.409
Male, n (%)	91 (51.7)	131 (52.6)	.231
Body mass index (kg/m^2)	29.6 (IQR, 26.3-32.5)	28.9 (IQR, 24.9-31.7)	.169
Diabetes mellitus, n (%)	15 (8.5)	18 (7.2)	.413
Hypertension, n (%)	76 (43.2)	105 (42.2)	.226
Hyperlipidemia, n (%)	87 (49.4)	84 (33.7)	.012
Smoking history, n (%)	46 (26.1)	71 (28.5)	.148
Alcohol consumption, n (%)	41 (23.2)	32 (12.9)	.016
Total cholesterol (mg/dL)	192 ± 57	186 ± 56	.076
Triglycerides (mg/dL)	134 ± 45	118 ± 36	.009
LDL-c (mg/dL)	115 ± 17	112 ± 16	.134
HDL-c (mg/dL)	54.3 ± 12.8	56.1 ± 13.9	.167
Neutrophils (10^9/L)	3.7 (2.9-4.6)	3.4 (2.6-4.1)	.012
Hs-CRP (mg/dL)	0.64 (0.31-3.24)	0.41 (0.22-2.19)	.006
Uric acid (mg/dL)	5.7 (4.1-6.7)	4.3 (3.6-5.3)	<.001
Febuxostat use, n (%)	81 (46.0)	71 (28.5)	.003
Antihypertensive use, n (%)	67 (38.1)	92 (36.9)	.462
Antiplatelet agents, n (%)	87 (49.4)	113 (45.4)	.116
Lowering lipid, n (%)	80 (45.4)	82 (32.9)	.024
HR_{pre} (bpm)	70.3 ± 11.2	68.6 ± 10.2	.103
HR_{post} (bpm)	131 ± 17	145 ± 18	.023
SBP_{pre} (mmHg)	128 ± 13	126 ± 12	.226
SBP_{post} (mmHg)	171 ± 21	168 ± 20	.171
LVEF (%)	64.2 ± 7.2	65.3 ± 8.3	.236
LAVi (mL/m^2)	23 ± 6	21 ± 5	.109
E/e'_{pre}	7.9 ± 1.9	7.2 ± 1.6	.243
E/e'_{post}	12.3 ± 2.8	8.1 ± 1.9	<.001

WDF, worsening of diastolic function; LDL-c, low-density lipoprotein; HDL-c, high-density lipoprotein; Hs-CRP, high-sensitivity C-reaction protein; HR, heart rate; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; LAVi, left atrial volume index.

Figure 4). After the stratification of patients into those with or without MACE, the level of SUA was still associated with MACE as shown by Cox proportional hazards analysis (HR=1.56 [1.03-2.89], *P*=.016). This was observed after the adjustment for confounding clinical and echocardiographic variables (Table 3).

Intra- and Interobserver Variation

Inter-observer measurement showed an ICC of 0.91 for LVEF, 0.89 for LAVi, 0.93 for E-wave, 0.90 for A-wave, and 0.92 for e'-wave. Similarly, intra-observer measurement showed an ICC of 0.92 for LVEF, 0.91 for LAVi, 0.91 for E-wave, 0.9 for A-wave, and 0.91 for e'-wave. This indicates satisfactory reproducibility of LVEF and diastolic function values.

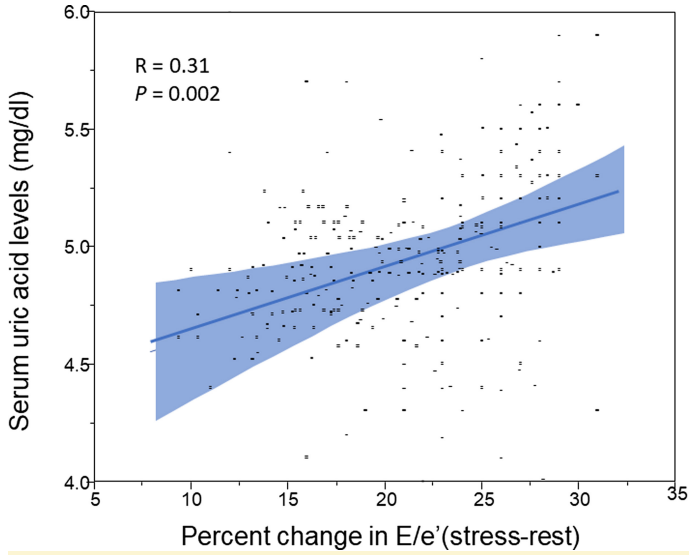

Figure 1. Increased serum uric acid levels are associated with percent change in E/e' (stress-rest).

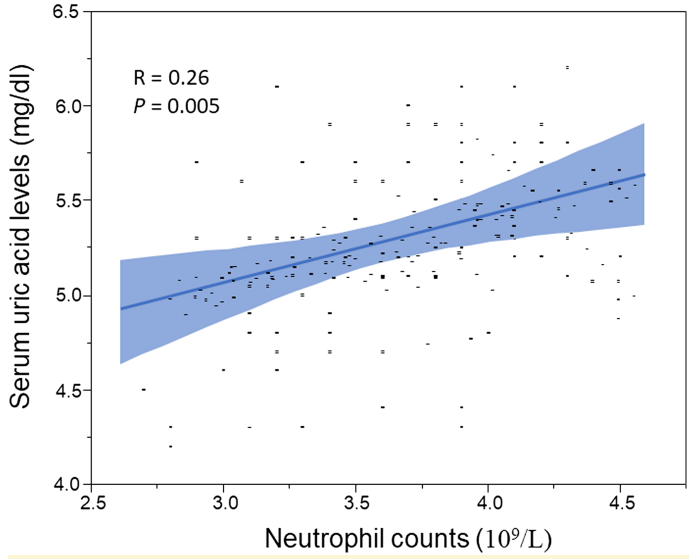

Figure 2. Neutrophil counts increase with increasing serum uric acid levels.

Discussion

To our knowledge, the associations between SUA, WDF, inflammatory markers, and MACE in CSF patients have not previously been reported. The principal findings were as follows: (1) uric acid was an independent predictor of WDF in patients with CSF; (2) SUA levels showed significant correlations with higher levels of biomarkers for inflammation in patients with WDF, but no significant correlations were seen in patients without WDF; (3) Increased SUA levels were independently associated with MACE in patients with CSF.

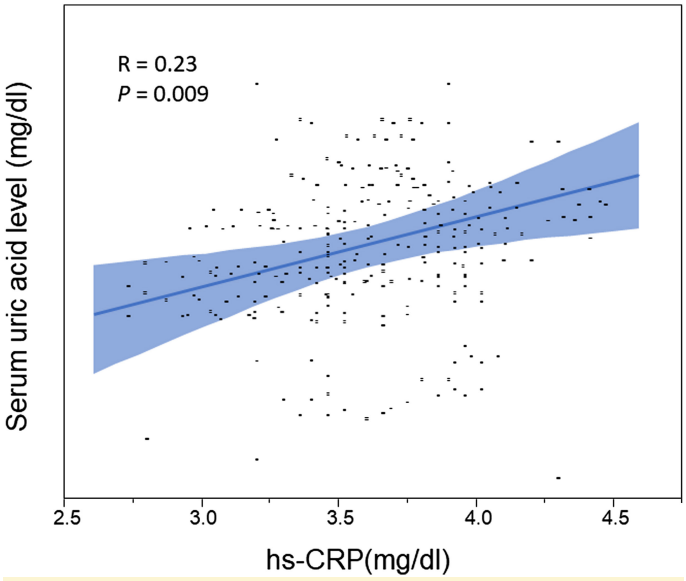

Figure 3. Increased hs-CRP levels are associated with increased serum uric acid levels. hs-CRP, high-sensitive C-reactive protein.

Table 2. Predictors of Worsening of Diastolic Function in Multivariate Analysis

Variables	Odds Ratio (95% CI)	*P*
Age	1.39 (0.92-3.57)	.213
Gender (male)	1.53 (0.72-3.14)	.156
Body mass index	1.38 (0.79-2.42)	.132
Hyperlipidemia	1.59 (0.89-3.16)	.197
Alcohol consumption	1.46 (0.76-3.09)	.126
Triglycerides	1.24 (0.81-2.87)	.152
Neutrophil counts	1.67 (0.91-3.08)	.085
Hs-CRP	1.48 (0.78-2.94)	.127
Uric acid	1.87 (1.17-3.82)	.023
Febuxostat use	0.83 (0.59-1.26)	.094

Hs-CRP, high-sensitivity C-reaction protein.

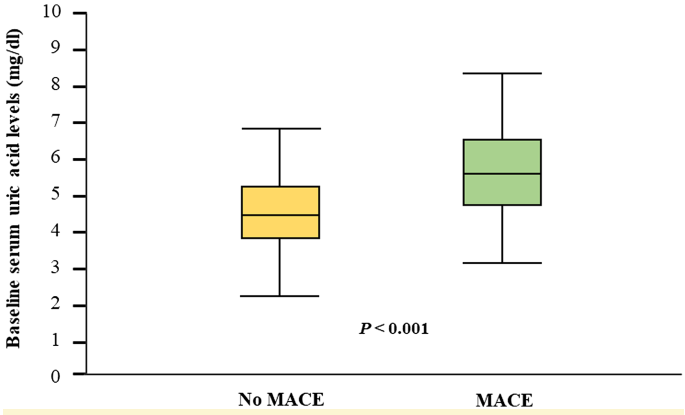

Figure 4. Baseline uric acid levels were significantly higher in patients who developed MACE than in patients who did not. MACE, major adverse cardiovascular event.

Table 3. Predictors of MACE at Univariate and Multivariable Analysis Stratified by With Versus Without MACE

	Univariate		Multivariate	
Variable	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Age	1.68 (0.91-4.27)	.167	1.31 (0.76-2.82)	.296
Gender (male)	1.43 (0.87-3.53)	.361	1.24 (0.86-2.67)	.316
Body mass index	1.46 (0.87-3.15)	.242	—	—
Hypertension	1.31 (0.79-2.59)	.285	—	—
Hyperlipidemia	1.72 (0.91-3.68)	.135	—	—
Alcohol consumption	1.63 (1.07-2.17)	.035	1.09 (0.83-2.76)	.295
Lowering lipid	1.23 (0.71-3.54)	273	—	—
Neutrophils	1.54 (1.14-3.69)	.021	1.48 (0.88-2.57)	.104
Hs-CRP	1.31 (1.06-3.19)	.017	1.39 (0.86-3.09)	.253
Uric acid	2.39 (1.37-5.32)	<.001	1.56 (1.03-2.89)	.016
Febuxostat use	0.71 (0.13-0.98)	.015	0.47 (0.23-1.37)	.132
LVEF	1.43 (0.89-2.67)	.132	—	—
LAVi	1.32 (0.93-2.81)	.106	—	—

MACE, major adverse cardiovascular events; Hs-CRP, high-sensitivity C-reaction; LVEF, left ventricular ejection fraction; LAVi, left atrial volume index.

Pathology studies have reported that patients with CSF show cellular edema and microvascular thickening with luminal narrowing and myofibril disorganization.[3,18] It is not yet clear whether these pathophysiologic alterations affect cardiac function. Currently, there is still controversy regarding whether patients with CSF have impairment of diastolic function, systolic function, or both.[4,19] Consistent with a previous study by Sezgin et al[20] who explored echocardiographic features in patients with CSF, we found that WDF occurred in 41.4% of CSF patients following exercise stress. However, there was not a significant difference in LVEF between resting and post-stress. This can be explained by the fact that exercise-induced ischemia increases the early filling pressures, thereby impairing left ventricle relaxation and giving rise to diastolic dysfunction.[7,21] A second explanation is that diastolic abnormalities arise before systolic changes in the ischemic cascade.[6,22] Since diastolic dysfunction eventually improves during rest, such functional impairment might be due to myocardial stunning.[23] In light of these findings, we believe that WDF in patients with CSF is in its early stages and patients with impaired exercise capacity require careful monitoring.

Previous studies reported that elevated SUA was linked to endothelial dysfunction and might therefore be an independent risk factor for CSF.[11] However, the underlying mechanism for this is still not known. So far, there are little data regarding how and to what degree the microvascular dysfunction and endothelial dysfunction affect LV function and exercise capacity in CSF patients.[2,13] The present study has now extended these earlier findings and shown for the first time a relationship between SUA and WDF in CSF patients. Our results showed that SUA was elevated in patients with WDF and that SUA was independently associated with WDF even after adjustment for other important factors. Hence, we speculate that endothelial dysfunction and microvascular dysfunction might arise due to elevated SUA through decreased nitric oxide bioavailability.[24,25] This can subsequently lead to myocardial stunning and WDF during stress conditions.[8] Based on this hypothesis, increased levels of SUA might be linked to endothelial dysfunction and hence indirectly associated with WDF. Serum uric acid therefore holds promise as a serum biomarker with potential application for risk stratification of CSF patients.

Additionally, inflammation may play an essential role in the link between SUA, endothelial dysfunction, and WDF.[26,27] In our study, neutrophil counts and the level of hs-CRP were both found to be significantly elevated in patients with WDF compared to those without. Moreover, elevated SUA levels were significantly related to neutrophil counts and hs-CRP in patients with WDF, which suggests a link between SUA and inflammation in this population. The present results concur with earlier work that linked increased SUA levels to biomarkers of inflammation.[10] Previous data suggested that uric acid could induce vessel inflammation and endothelial dysfunction, thus concomitantly leading to the development of atherosclerosis and likely explaining the myocardial ischemia and WDF seen in patients with CSF.[8] Once ingested by endothelial cells via specific transporters, uric acid could induce inflammation, oxidative stress, and dephosphorylation of nitric oxide synthase, thus resulting in endothelial dysfunction via smooth muscle cell proliferation or the production of angiotensin II.[28] In support of this, other studies have shown that lowering of uric acid levels attenuates inflammation via activation of the AMPK pathway.[26]

Several previous studies have examined possible associations between SUA and cardiovascular disease or the mortality risk from all causes in specific disease populations or in the general population.[9,29] The relationship between SUA and MACE in CSF patients has not previously been reported. However, we found that SUA independently predicted MACE in CSF patients, even after adjusting for potential confounders. This might be explained by uric acid exerting an inflammatory effect on endothelial and vascular smooth muscle cells, thereby causing an increased expression of chemokines and cytokines.[30,31] The present study also supports an earlier study showing that endothelial dysfunction was an early phase of atherosclerosis and uric acid was linked to dysfunction of the coronary microvasculature and poor outcome in postmenopausal women.[10] These events may be secondary to inflammation, as seen by the elevated levels of inflammatory markers. These findings might help to guide decision-making for therapy and for counseling of patients.

There are several limitations to this study. The sample size of our cohort was relatively small, and hence, larger studies are needed to confirm the present findings. Despite performing multivariate analysis and adjusting for various confounding factors, no corrections were made for other unmeasured variables that could have influenced the results. Finally, there may be minor problems with the accuracy of some of the echocardiographic measurements (such as LVEF or LAVi) due to image quality or distortions in LV geometry.

Conclusion

The current study demonstrated that SUA is an independent predictor of WDF after exercise stress and may be mediated by inflammation. Furthermore, SUA is associated with MACE in CSF patients. The measurements of inflammation biomarkers and uric acid could help to understand the underlying mechanism of coronary atherosclerosis and to predict its progression in CSF patients. Additional prospective trials are required to explore therapies that lower uric acid levels in order to manage cardiovascular risk in this population.

Ethics Committee Approval: The study was approved by the medical ethics committee of Capital Medical University (No: IR.IEC-C-009-A04-V.03.2).

Informed Consent: Written informed consent was obtained from the patients of the study.

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