Relationship between Serum Uric Acid and Coronary Blood Flow in Patients with Atrial Fibrillation

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Abstract

Objectives: Atrial Fibrillation (AF) is associated with impaired coronary flow by means of Thrombolysis in Myocardial Infarction (TIMI) Frame Count (TFC). The Serum Uric Acid (SUA) level is elevated in patients with AF. In the present study we aimed to investigate the relationship between serum uric acid and TFC in patients with AF in the absence of obstructive Coronary Artery Disease (CAD).

Methods: This observational study enrolled 185 AF patients and 189 control subjects, all with angiographically documented normal coronary arteries. Serum uric acid was measured at baseline and mean TFC was assessed after diagnostic coronary angiography.

Results: The SUA was 6.3 ± 1.0 mg in the AF group and 4.9 ± 1.1 mg in the control group ($p<0.001$). In AF patients, SUA was significantly correlated with mean TFC ($r=0.477$, $p<0.001$). In linear regression analysis, SUA and low-density lipoprotein were found to be independently associated with mean TFC ($p<0.001$ and $p<0.05$ respectively).

Conclusion: Serum uric acid seems to be independently associated with coronary blood flow in patients with atrial fibrillation in the absence of obstructive coronary artery disease.

Keywords: Atrial fibrillation; Serum uric acid; TIMI frame count; Coronary flow; Coronary angiography

Introduction

Oxidative stress plays an important role in the development of endothelial dysfunction. The Xanthine Oxidase (XO) pathway is one of important systems generating vascular oxidative stress. XO is an enzyme that produces Uric Acid (UA) during purine catabolism, and oxygen free radicals are generated [1]. Thus, the UA reflects level of oxidative stress.

UA is a strong risk factor for development of cardiovascular condition such as Myocardial Infarction (MI) and stroke [2]. Recently a number of studies have reported that elevated levels of UA are associated not only with the presence of cardiovascular disease but also with poor prognosis in the setting of stroke and in the patients without coronary artery disease [3-7]. Compared with subjects in sinus rhythm, the UA is elevated in patients with Atrial Fibrillation (AF) [8,9].

AF is associated with impaired coronary flow and diminished myocardial perfusion [10-12]. In a previous study, we demonstrated that patients with AF in the absence of obstructive coronary artery disease have significantly higher Thrombolysis in Myocardial Infarction (TIMI) Frame Count (TFC) for all three coronary vessels compared to the control subjects without atrial fibrillation [10]. However, the clinical implications of the increased TFC in AF patients have not been fully elucidated, although it has been reported that impaired coronary blood flow is associated with unfavourable outcomes in patients with AF [12].

The purpose of the current study was to investigate whether there would be a correlation between SUA and TFC in patients with AF.

Methods

Patient population and study protocol

The present observational study was conducted in the department of cardiology, the first affiliated hospital of Sun Yat-sen University. From January 2008 to March 2012, we prospectively screened all consecutive patients who were referred for diagnostic coronary angiography. The study population was expanded from our recent study [10] on the relation between AF and coronary flow, evaluated by TFC method.

All patients with a history of AF and in AF rhythm during the angiography were initially included in the current study. AF was diagnosed and categorised according to the American Heart Association/American College of Cardiology/European Society of Cardiology criteria [13]. AF was defined as having typical disorganised atrial activity on the 12-lead electrocardiogram (ECG). Paroxysmal AF was defined as AF episodes that terminated spontaneously and generally lasted seven days or less (most less than 24h), and persistent AF was defined as sustained AF that persisted continuously for more than seven days. In the present study, it was termed long-standing AF when lasted longer than one year, and the category of permanent AF included cases of long-standing AF in which cardioversion has failed or has not been attempted. Subjects with any of the following were excluded from the study: documented CAD in history (i.e. previous myocardial infarction, percutaneous or surgical coronary revascularisation, and/or one or more angiographically documented coronary stenosis ≥ 50% luminal diameter), structural heart disease on echocardiography, myocardial or pericardial disease, chronic obstructive pulmonary disease, hyperthyroidism, renal and hepatic dysfunction, patients after pacemaker or cardioverter-defibrillator implantation, or any history of collagen vascular disease and malignancy.

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The initial control group was made up of age- and gender-matched patients (by a ratio of 2:1 with the AF group) without any history of AF who were referred for diagnostic coronary angiography in the same period, using identical exclusion criteria.

Clinical history and characteristics were retrieved using patient medical records of the hospital information system. Duration of AF was determined as precisely as possible by previous electrocardiograms, 24-hour Holter registrations, and by the patient's history. Baseline was defined as the moment at which the cardiologist decided to refer the patient for diagnostic coronary angiography.

The study was approved by the institutional research ethics committee. All participants signed an informed consent before angiography.

Blood sampling

Blood samples were obtained following an overnight fasting state. Blood samples were centrifuged at 3000 rpm for 10 min. Plasma samples were stored at -70°C until analysis for UA, hsCRP, triglyceride, total cholesterol, LDL, High density Lipoprotein (HDL), and fasting glucose.

Measurement of biochemical markers

Samples of peripheral venous blood were drawn from the antecubital vein at admission. Serum levels of fasting blood glucose, total cholesterol, triglyceride, Low-Density Lipoprotein (LDL) cholesterol, High-Density Lipoprotein (HDL) cholesterol, uric acid, and creatinine concentrations were measured with an automated chemistry analyzer (Abbott, Aeroset, MN, USA) using commercial kits (Abbott, USA).

Transthoracic echocardiography

All study participants underwent transthoracic echocardiographic examination within three days before angiography. The left atrial diameter was measured in the M mode. Left ventricular end-diastolic and end-systolic diameters were measured from the M-mode trace obtained from the parasternal long-axis view. Left ventricular ejection fraction was measured by the Simpson method.

Coronary Angiography and Documentation of TIMI Frame Count (TFC)

In all study participants, selective coronary angiography was performed using standard Judkins technique. Coronary arteries were visualised in left and right oblique planes with cranial and caudal angulations. Injection of contrast medium (Iopromide, Ultravist-370; Schering AG, Berlin, Germany) was carried out by an automatic injector, at a speed of 5 mL/s for left coronary artery and 3 mL/s for right coronary artery, and all angiograms were filmed at a speed of 30 frames/s. Significant or obstructive coronary artery disease was defined as a ≥50% luminal stenosis in at least one major epicardial coronary artery.

Coronary flow was quantified using the TIMI frame count method, described by Gibson et al. [14,15]. The first frame was defined as the frame in which concentrated dye occupies the full width of the proximal coronary artery lumen, touching both borders of the lumen, and indicates forward motion down the artery. The final frame counted is that in which the contrast first reaches the distal predefined landmark branch without the necessity for full opacification. Standard distal coronary landmarks used for analysis were as follows: the distal bifurcation for the Left Anterior Descending Coronary Artery (LAD), commonly referred as the "mustache", "pitchfork" or "whale's tail"; the distal bifurcation of the segment with the longest total distance for the Left Circumflex Coronary Artery (LCX); and the first branch of the posterolateral artery for the Right Coronary Artery (RCA). The TFC in LAD and LCX were assessed in a right anterior oblique view with caudal angulation, and that in RCA was assessed in a left anterior oblique projection with cranial angulation. As the LAD is usually longer than the other major coronary arteries, the LAD frame count was divided by 1.7 to derive the corrected TFC as described earlier [14,15]. The mean TFC for each participant was calculated by dividing the sum of the TFC of LAD (corrected), LCX and RCA by 3.

TFC was assessed objectively by two independent observers, who were blinded to the clinical details of the individual participants. Two assessments were performed independently, and the mean value of the two measurements was accepted as final value of TFC.

Statistical analysis

The statistical analysis was performed using SPSS 10.0 software. Continuous data are presented as means ± standard deviations and categorical variables are presented as percentages. Continuous variables between groups were compared by Student's t test. Proportions were compared by the Fisher exact test when the expected frequency was <5, otherwise the chi-square test was applied. The Spearman correlation test was used to determine the relation between mTFC and clinical and laboratory parameters. In order to determine independent associates of mTFC, we performed multivariate stepwise linear regression analysis, including mean TFC as dependent and clinical and laboratory parameters as independent variables. Significance was considered to be achieved for two-tailed p values <0.05.

Results

Study population and clinical demographics

Between January 2008 and March 2012, 262 patients with a history of AF and in AF rhythm during the angiography were referred for diagnostic coronary angiography in our cardiac catheter laboratory. Among these patients, 45 were excluded for the presence of the exclusion criteria as described above. Thus, the remaining 217 patients comprised the initial AF group, and the initial control group consisted of 434 age- and gender-matched subjects without any history of AF.

During diagnostic CAG, significant CAD was detected in 32 patients in the AF group and in 245 in the control group (14.7% vs. 56.4%, p<0.001). Thus, the participants without significant CAD constituted the final study population, with 185 in the AF group and 189 in the control group.

Of all the 185 AF patients, 76 (41%) were classified as paroxysmal AF, 72 (39%) as persistent AF, and 37 (20%) as long-standing or permanent AF. Median duration of the history of AF was 26 months (range 0-288 months).

Patients' clinical demographics, characteristics for echocardiography and the use of medications in the two groups are depicted in Table 1.

The two groups were similar for age, gender, cardiovascular risk factors, clinical and echocardiographic parameters, except that patients in the AF group had lower systolic blood pressure and left ventricular ejection fraction, and higher heart rate and left atrium diameter.

Comparison of blood parameters and tfc between the study groups

When compared with the control group, the patients with AF had higher levels of SUA ($p<0.001$). Patients with AF also had higher creatinine and low-density lipoprotein levels than control group ($p<0.05$ and $p<0.05$, respectively). As expected, the TFC for all the epicardial coronary arteries and the mean TFC value were significantly higher in the patients with AF than the control group ($p<0.001$, for all) (Table 2).

Association between mtfc and clinical and laboratory parameters in af patients

Correlations between mTFC and clinical and laboratory parameters were shown in Table 3. Uric acid and low-density lipoprotein were found to be positively correlated with mean TFC.

To find out the independent associates of mean TFC, multivariate stepwise linear regression analysis was performed using mean TFC as the dependent and all the clinical and echocardiographic parameters as independent variables. Among all these variables, Uric acid and low-density lipoprotein were found to be associated independently with mean TFC (Table 4).

Discussion

This is the first report showing that uric acid is significantly and independently related with coronary blood flow in patients with Atrial Fibrillation (AF).

TIMI frame count is a simple, objective, and reproducible method for quantifying coronary blood flow during coronary angiography [14,15], currently being used as a surrogate marker for epicardial coronary blood velocity and microvascular status [16,17].

The changes of uric acid in patients with AF had not been investigated until recent years. Liu et al.[18] First reported that patients with AF had a higher level of UA, there was an independent relationship between high serum uric acid and AF. Tamariz et al. [19] indicated that elevated SUA is associated with a greater risk of AF, particularly among blacks and women. Chao et al. [20] suggested that hyperuricemia was associated with a larger left atrial size and may be a novel risk factor for the development of AF. In accordance with these reports, our present study found that the UA was significantly higher in AF patients than in control subjects.

It is well established that the endothelium plays an important role in the control of coronary blood flow by regulating coronary vascular resistance [21]. It has been reported that uric acid induces intracellular oxidative stress and inflammation [22,23]. Oxidative stress may impair endothelial function and coronary blood flow in angiographically normal coronary arteries [24,25]. It has been reported that UA level was significantly associated with coronary blood flow and that elevated

Variables	AF Group (n = 185)	Control Group (n = 189)	p Value
Age, y	65.9 ± 10.1	65.7 ± 10.3	0.957
Male gender, n (%)	116 (62.7%)	115 (60.8%)	0.712
Risk factors for coronary artery disease, n (%)			
Systemic hypertension	102 (55.1%)	97 (51.3%)	0.460
Diabetes mellitus	31 (16.8%)	35 (18.5%)	0.655
Hypercholesterolaemia	49 (26.5%)	63 (33.3%)	0.148
Current smokers	42 (22.7%)	54 (28.6%)	0.194
Family history of coronary disease	22 (11.9%)	21 (11.1%)	0.813
Baseline blood pressure and heart rate			
Systolic blood pressure, mmHg	127.8 ± 13.3	130.6 ±14.5	0.005
Diastolic blood pressure, mmHg	72.9 ± 10.1	73.8 ±10.6	0.479
Heart rate, beats/min	80.6 ±13.8	72.4 ± 12.7	<0.001
Echocardiographic parameters			
Left atrium diameter (parasternal axis), mm	38.3 ± 6.4	34.8 ± 5.9	<0.001
Left ventricular end-diastolic diameter, mm	51.1 ± 9.6	49.6 ± 9.7	0.062
Left ventricular end-systolic diameter, mm	33.3 ± 5.9	32.7 ± 6.4	0.173
Interventricular septum thickness, mm	11.6 ± 1.6	11.5 ± 1.5	0.297
Posterior wall thickness, mm	10.0 ± 1.3	9.9 ± 1.2	0.284
Left ventricular ejection fraction, %	54.2 ± 10.5	57.9 ± 10.3	<0.001
Baseline use of medication, n (%)			
Digoxin	39 (21.1%)	18 (9.5%)	0.002
Aspirin	142 (76.8%)	157 (83.1%)	0.127
Clopidogrel	130 (70.3%)	147 (77.8%)	0.098
Statins	77 (41.6%)	91 (48.1%)	0.205
Beta-blockers	82 (44.3%)	77 (40.7%)	0.483
ACE inhibitors and/or ARBs	75 (40.5%)	82 (43.4%)	0.577
Calcium channel blockers	57 (30.8%)	61 (32.3%)	0.761
Diuretics	45 (24.3%)	41 (21.7%)	0.545
Nitrates	36 (19.5%)	35 (18.5%)	0.817

Values are given as number of patients (%) or mean ± SD

ACE: angiotensin-converting enzyme; ARB: Angiotensin II Receptor Blocker.

Table 1: Clinical and Echocardiographic Characteristics in the AF and Control Groups. Values are given as number of patients (%) or mean±SD. ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker.

Variables	AF Group (n = 185)	Control Group (n = 189)	p Value
Glucose, mg/dl	111.5 ± 28.9	108.2 ± 33.4	0.310
Total cholesterol, mg/dl	200.2 ± 31.8	196.1 ± 31.5	0.207
LDL, mg/dl	133.0 ± 31.8	124.1 ± 36.4	<0.05
HDL, mg/dl	45.4 ± 8.9	44.2 ± 8.4	0.169
Triglyceride, mg/dl	174.7 ± 49.6	178.4 ± 56.4	0.493
Uric acid, mg/dl	6.3 ± 1.0	4.9 ± 1.1	<0.001
Creatinine, mg/dl	0.78 ± 0.12	0.73 ± 0.09	<0.05
TIMI frame count			
Corrected TFC for left anterior descending artery	33.0 ± 10.6	24.6 ± 10.2	<0.001
TFC for left circumflex artery	31.5 ± 9.9	23.6 ± 9.3	<0.001
TFC for right coronary artery	31.8 ± 9.7	23.9 ± 9.0	<0.001
Mean TIMI frame count	32.1 ± 9.3	24.1 ± 8.7	<0.001

Values are given as mean ± SD

LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TFC: TIMI frame count

Table 2: Blood Test and TIMI Frame Count in the AF and Control Groups.

Variables	Mean TFC	
	r	p Value
Systolic blood pressure	0.051	0.488
Heart rate	0.095	0.198
Left atrium diameter	0.033	0.658
Left ventricular ejection fraction	0.144	0.066
Digoxin	0.135	0.068
LDL	0.223	<0.05
Uric acid	0.477	<0.001
Creatinine	0.084	0.258

LDL: Low-Density Lipoprotein, TFC: TIMI Frame Count

Table 3: Relationship between the mean Thrombolysis In Myocardial Infarction Frame Count (TIMI) and clinical and laboratory parameters

Variables	Unstandardised		Standardised	95% CI		p Value
	β	Std. error	β	L	U	
Urid acid	2.704	0.687	0.277	1.348	4.060	<0.001
low-density lipoprotein	0.146	0.063	0.164	0.022	0.269	<0.05

Table 4: The stepwise linear regression of mean TFC in AF Patients.

UA level might be an independent predictor for the presence of slow coronary flow [26]. The generation of oxygen free radicals during production of UA, is one of the underlying causes of impaired coronary flow after primary PCI [27]. Akpek et al. showed a high plasma UA levels were independent predictors of no-reflow post primary PCI [28]. Elbasan et al. [29] showed that the UA level was independently associated with slow coronary flow in patients of cardiac syndrome X. Thus, these findings suggest that UA may to some extent reflect function of endothelium and microcirculation.

Atrial fibrillation is associated with impaired coronary flow by means of Thrombolysis in Myocardial Infarction (TIMI) Frame Count (TFC) [10]. In AF patients, however, the correlation between UA and coronary blood flow has never been investigated. For the first time, our present study demonstrated an independent association between serum uric acid and coronary flow, by means of TFC method, in AF patients without obstructive coronary artery disease.

Considering that serum uric acid is a potentially useful prognostic biomarker in patients with cardiovascular diseases [1,26], our findings suggest that in AF patient decreasing UA may improve coronary blood flow, evaluated by TIMI frame count method, which may have some clinical significance, which should be furtherly confirmed by relevant researches.

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