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The role of urotensin II and atherosclerotic risk factors in patients with slow coronary flow

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Abstract: *Background:* Slow coronary flow (SCF) is an angiographic finding characterized with delayed opacification of epicardial coronary arteries without obstructive coronary disease. Urotensin II (UII) is an important vascular peptide, which has an important role in hypertension, coronary artery disease, and vascular remodeling in addition to potent vasoconstrictor effect. *Objectives:* We investigated UII levels, hypertension, and other atherosclerotic risk factors in patients with SCF, a variety of coronary artery disease. *Methods:* We enrolled 14 patients with SCF and 29 subjects with normal coronary arteries without SCF. We compared the UII levels and the atherosclerotic risk factors between patients with SCF and control subjects with normal coronary flow. *Results:* UII concentrations were significantly higher in patients with SCF compared to controls (711.0 ± 19.4 vs. 701.5 ± 27.2 ng/mL, $p = 0.006$). We detected a positive correlation between SCF and age ($r = 0.476$, $p = 0.001$), BMI ($r = 0.404$, $p = .002$), UII concentrations ($r = 0.422$, $p = 0.006$), and hypertension ($r = 0.594$, $p = 0.001$). *Conclusion:* We identified increased UII levels in patients with SCF. We think that UII concentrations may be informative on SCF pathogenesis due to relationship with inflammation, atherosclerosis, and vascular remodeling.

Keywords: slow coronary flow, urotensin II, atherosclerosis, atherosclerotic risk factors, CRP

Introduction

Slow coronary flow (SCF) is an angiographic finding characterized with delayed opacification of epicardial coronary arteries without obstructive coronary disease [1]. SCF is a relatively common angiographic finding with a reported incidence of 1% in patients undergoing coronary angiography for the suspicion of coronary artery disease (CAD) [2]. Since the first description in 1972 by Tambe et al. [1], only a limited number of studies have focused on SCF; therefore, the precise pathophysiological mechanisms and the clinical importance of SCF are not fully understood at the moment. Several mechanisms have been proposed for SCF phenomenon including small vessel disease, microvascular vasomotor dysfunction, diffuse atherosclerosis, and endothelial dysfunction [3–6]. Occlusive disease of the small coronary arteries, which may be a form of early phase atherosclerosis, has also been suggested as a cause [7]. Moreover, SCF may cause transient myocardial hypoperfusion in patients with angina and normal coronary arteries, and these patients have higher probability of significant CAD and an apparently worse prognosis [8].

Urotensin II (UII), an undecapeptide cleaved from a precursor protein, promotes vasoconstriction and vascular smooth muscle cell proliferation [9, 10]. UII is one of the most important and the most studied peptide involved in vascular remodeling. UII, a potent vascular constrictor, is up-regulated in patients with hypertension, and atherosclerosis in addition to relevant receptors [11–13].

Even though, the pathophysiological impact of UII in atherosclerosis and coronary artery disease has been

studied extensively, the role of UII in SCF as a different variety of atherosclerosis has not been clarified so far. We think that pro-atherosclerotic and inflammatory actions of UII may also act in SCF pathogenesis. Therefore, we intended to investigate UII concentrations and atherosclerotic risk factors in patients with SCF compared to control subjects with normal coronary flow (NCF).

Methods

Patient population and study protocol

Our study was prospective and cross sectional. Among 2,049 patients, coronary angiography procedures performed between September 2010 and 2011 in our hospital, we selected patients with the presence of typical stable angina pectoris and positive or equivocal results in non-invasive stress tests as the indication. Patients with obstructive CAD, left ventricular dysfunction, left ventricular hypertrophy, atrial fibrillation, valvular heart disease, pericardial and myocardial diseases, renal dysfunction (creatinine >1.5 mg/dL), anemia, thrombocytopenia, hepatic dysfunction, neoplasms, recent major surgical operation, and accompanying inflammatory diseases such as hemolytic and autoimmune disorders were excluded.

We excluded 823 patients with acute coronary syndromes. Following the careful review of remaining 1,226 patients, we identified 14 (6 males) patients with SCF. We enrolled subjects with normal coronary arteries and flow consecutively in a ratio of 1:2. Thus, 29 patients (11 males) who had normal coronary angiograms and flow were enrolled as control subjects. UII levels were measured in all subjects and compared between groups. The study has been approved by the local ethics committee and is in accordance with the Declaration of Helsinki. All patients gave informed consent before participation. Medical histories were taken and thorough examination was performed.

Hypertension was acknowledged if the patient was on antihypertensive medication or if systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or both were observed during examination. Diabetes mellitus was considered if fasting blood glucose was >126 mg/dL or if the patient was on antidiabetic therapy. Patients who were using tobacco products on admission to our hospital and those quitted smoking within the last year were considered as smokers.

Coronary angiography and determination of SCF

Standard selective coronary angiography with at least four views of the left coronary artery and two views of the right coronary artery (RCA) were performed using the Judkins technique and 6-French right and left heart catheters without the use of nitroglycerin. All procedures were performed via femoral access site. Coronary angiograms

were recorded in the right and left oblique planes using cranial and caudal angulations at a rate of 30 frames/s. During coronary angiography, iopromide (Ultravist 370, Schering AG, Berlin, Germany) was used as the contrast agent in all patients. The patients were assessed for the presence of SCF during coronary angiography and coronary flow rates were quantified by the thrombolysis in myocardial infarction (TIMI) frame count (TFC) method. For objective quantification of the coronary flow, two independent observers blinded to the clinical data of the study participants assessed the coronary flow in coronary arteries using TFC [14]. This method establishes the number of cine frames, recorded at 30 frames/s, required for the contrast to reach standard distal coronary landmarks in the left anterior descending artery (LAD), left circumflex artery (LCx), and RCA. Predefined distal landmarks are the distal bifurcation for the LAD, commonly referred to as the "pitchfork" or "whale's tail," the distal bifurcation of the segment with the longest total distance for the LCx, and the first branch of the posterolateral artery for the RCA. The standard mean values for normal visualization of coronary arteries are described as 36.2 ± 2.6 frames for LAD, 22.2 ± 4.1 frames for LCx, and 20.4 ± 3.0 frames for RCA. As the LAD is usually longer than the other major coronary arteries, the TFC for this vessel is often higher. Therefore, the TFC for LAD is divided by 1.7 to obtain the corrected TFC (cTFC). The standard corrected mean value (cTFC) for LAD coronary artery is 21.1 ± 1.5 frames. All participants with a TFC greater than the two standard deviations of the previously published range for the particular vessel were considered to have SCF [14]. The mean TFC for each patient and control participant was calculated by dividing the sum of the TFC of the corrected LAD, LCx, and RCA by three.

Biochemical analyses

Blood samples were drawn by venipuncture to measure routine blood chemistry parameters after fasting for at least 8 h. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were recorded. Glucose, creatinine, and lipid profile were determined by standard methods. Serum C-reactive protein (CRP) was analyzed using a nephelometric technique (Beckman Coulter Immage 800; Fullerton, CA, USA; normal range: 0–0.8 mg/dL).

Measurement of UII

We collected blood samples from the antecubital vein of subjects after overnight fasting to measure blood biochemical parameters, including plasma UII levels. Blood was drawn into the tubes containing disodium

ethylenediaminetetraacetic acid (1 mg/mL) and aprotinin (500 U/mL; Sigma-Aldrich, St. Louis, MO, USA), then centrifuged immediately at $3,500 \times g$ for 10 min at 4 °C; plasma was stored at −80 °C for assay. UII levels were measured by radioimmunoassay (RIA). In brief, samples extracted through a Sep-Pak C18 cartridge were assayed by the use of an RIA kit (Phoenix Pharmaceuticals, Belmont, CA, USA). For the UII immunoreactivity assay, the cross-reactivity with human UII was 100%. The intra- and inter-assay coefficients of variation of UII for blood samples were both <10%.

Statistical analysis

The SPSS statistical software (SPSS 15.0 for windows, SPSS Inc., Chicago, IL, USA) was used for all statistical calculations. Continuous variables were given as mean ± SD or median (interquartile range) as appropriate; categorical variables were defined as percentage. Data were tested for normal distribution using the Kolmogorov–Smirnov test. The Student's t-test was used for the univariate analysis of normally distributed continuous numerical variables and Mann–Whitney U test was used for non-normally distributed numerical variables, and the χ^2-test for the categorical variables. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$.

Results

UII concentrations were significantly higher in patients with SCF compared to controls (711.0 ± 19.4 vs. 701.5 ± 27.2 ng/mL, $p = 0.006$). Moreover, patients with SCF tended to be older (55 ± 12 vs. 42 ± 11 years, $p = 0.001$), and have a higher body mass index (BMI) (30 ± 4 vs. 26 ± 4 kg/m², $p = 0.002$), and more prevalent hypertension (64% vs. 10%, $p = 0.001$). Remaining basal characteristics and atherosclerotic risk factors were similar between groups. We detected a positive correlation between SCF and age ($r = 0.476$, $p = 0.001$), BMI ($r = 0.404$, $p = 0.002$), UII concentrations ($r = 0.422$, $p = 0.006$), and hypertension ($r = 0.594$, $p = 0.001$) (*Fig. 1*, *Tables I* and *II*).

Discussion

In this study, we revealed significantly higher UII levels in patients with SCF compared to patients with angiographically normal coronary arteries and NCF. Moreover, we detected that SCF significantly associated with hypertension, advanced age, and obesity.

Although the exact mechanism of SCF is not consistently determined, there are several suggested mechanisms involved in the pathogenesis of SCF. The first hypothesis that small vessel dysfunction contributes
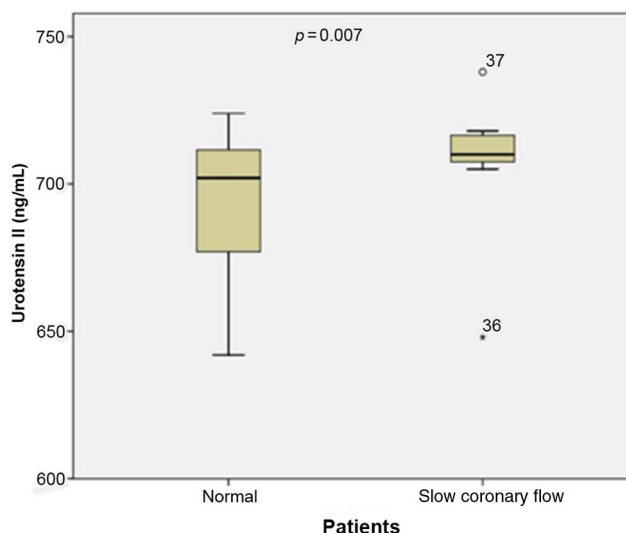

Fig. 1. UII concentrations in patients with SCF and control group

to the pathogenesis of SCF was proposed by Tambe et al. [1] and was confirmed by Mangieri et al. [3], who demonstrated microvascular abnormalities in patients with SCF [3]. Their histopathological examinations showed evidence of small vessel abnormalities such as endothelial thickening due to cell edema, capillary damage, and reduced luminal diameter of the small vessels. In addition, Kurtoğlu et al. [15] reported an improvement in microvascular tone and coronary flow with microvascular vasodilators, implying a functional increase in microvascular resistance. On the contrary, intravascular ultrasound examinations identified epicardial CAD as a pathophysiological factor for SCF, in addition to microvascular disease [4]. Abnormal slow flow pattern in coronary arteries has been deduced to be a manifestation of diffuse atherosclerotic disease due to endothelial injury without creating an angiographically visible coronary lesion [16]; therefore, SCF may be an early manifestation of diffuse atherosclerosis involving both microvascular system and epicardial coronary arteries [4]. In addition, inflammation [17, 18], platelet function disorder [19, 20], and imbalance of vasoactive substances [15, 21] have also been blamed in the pathogenesis of the SCF phenomenon. Serum paraoxonase (PON), a high-density lipoprotein bound antioxidant enzyme, acts against atherosclerosis and endothelial dysfunction. Yıldız et al. [22] reported an independent association between serum PON activity with the mean TFC, suggesting that reduced serum PON activity may be a biochemical marker of SCF. Enli et al. [23] demonstrated significantly increased serum malondialdehyde, erythrocyte superoxide dismutase, and decreased erythrocyte-reduced glutathione levels in patients with SCF compared to patients with NCF. These findings indicate that free radical damage as well as endothelial dysfunction may also take place in the pathogenesis of SCF. In contrast to these data,

Table I | Baseline characteristics of the study population

Parameters ($n = 43$)	SCF group ($n = 14$)	Control group (NCF, $n = 29$)	p value
Age (years ± SD)	55 ± 12	42 ± 11	0.001
Sex (male), n (%)	6 (43)	11 (38)	0.821
Body mass index	30 ± 4	26 ± 4	0.002
Hypercholesterolemia, n (%)	7 (50)	11 (38)	0.532
Family history of CAD, n (%)	7 (50)	10 (35)	0.334
Smoking, n (%)	4 (29)	8 (28)	0.902
HT, n (%)	9 (64)	3 (10)	0.001
Diabetes mellitus, n (%)	2 (14)	4 (14)	0.936
Hemoglobin (g/dL)	13.9 ± 1.2	13.5 ± 1.3	0.506
Total cholesterol (mg/dL)	195 ± 50	188 ± 35	0.639
LDL (mg/dL)	129 ± 45	119 ± 32	0.143
HDL (mg/dL)	40 ± 9	45 ± 9	0.428
Triglycerides (mg/dL)	144 ± 105	141 ± 63	0.929
Urotensin II (ng/mL) [median ± IQR]	711.0 [700–721]	701.5 [666.5–736.5]	0.006
Glucose (mg/dL) [median ± IQR]	103 [76–130]	94 [81–107]	0.050
Creatinine (mg/dL) [median ± IQR]	0.78 [0.67–0.89]	0.75 [0.6–0.9]	0.536
TIMI frame count measurements			
LAD	31 ± 7	61 ± 30	0.001
LAD (corrected)	19 ± 4	35 ± 18	0.001
LCx	23 ± 6	32 ± 14	0.005
RCA	21 ± 5	43 ± 23	0.001
Mean	22 ± 4	37 ± 14	0.001

SCF, slow coronary flow; UII, urotensin II; HT, hypertension; SD, standard deviation; NCA, normal coronary flow (control group); CAD, coronary artery disease; TIMI, thrombolysis in myocardial infarction; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; IQR, interquartile range

Table II | Correlations of SCF and UII with the study parameters

Parameters	SCF	Age	BMI	UII	HT
SCF	–	$r = 0.476$ $p = 0.001$	$r = 0.404$ $p = 0.002$	$r = 0.422$ $p = 0.006$	$r = 0.564$ $p = 0.001$
Age	$r = 0.476$ $p = 0.001$	–	$r = 0.481$ $p = 0.001$	$r = 0.075$ $p = 0.634$	$r = 0.590$ $p = 0.000$
BMI	$r = 0.404$ $p = 0.002$	$r = 0.481$ $p = 0.001$	–	$r = 0.037$ $p = 0.814$	$r = 0.493$ $p = 0.001$
UII	$r = 0.422$ $p = 0.006$	$r = 0.075$ $p = 0.634$	$r = 0.037$ $p = 0.814$	–	$r = 0.230$ $p = 0.138$
HT	$r = 0.564$ $p = 0.001$	$r = 0.590$ $p = 0.000$	$r = 0.493$ $p = 0.001$	$r = 0.230$ $p = 0.138$	–

SCF, slow coronary flow; UII, urotensin II; HT, hypertension; BMI, body mass index

recently, Kopetz et al. [24] could not demonstrate any differences in endothelial function, inflammatory proteins (myeloperoxidase and high-sensitivity CRP), oxidative stress biomarkers (malondialdehyde and homocysteine), and asymmetric dimethylarginine levels in patients with SCF compared to healthy controls. Therefore, the mechanisms and pathogenesis of SCF remain controversial.

UII induces potent vasoconstriction and vascular smooth muscle cell proliferation. The UII receptor–UII interaction stimulate the release of calcium (Ca^{2+})

in vascular smooth muscle cells through inositol tri-phosphate and diacylglycerol. Increased intracellular calcium concentrations lead to cellular proliferation and activation of Ca^{2+}-dependent kinases via calmodulin binding [25].

Recent studies have shown that UII may have additional negative influence on vascular remodeling. UII and angiotensin II affect vascular endothelial growth factor (VEGF) expression in adventitial fibroblasts that have an important role in vascular remodeling. Although the exact role of VEGF in vascular remodeling induced by UII is still not clarified, adventitial fibroblast proliferation and increased collagen synthesis may ensue [26].

Studies investigating the association between UII and atherosclerosis have revealed raised plasma UII levels in patients with vascular disorders such as essential hypertension, diabetes mellitus, atherosclerosis, ischemic heart disease, and heart failure. UII is synthesized in endothelial cells, smooth muscle cells, and infiltrating macrophages of atherosclerotic lesions. Inflammation upregulates urotensin receptor expression. Stimulation of receptor by UII leads to endothelial and smooth muscle cell proliferation, foam cell formation, and chemotaxis via vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 expression. In addition, UII produces reactive oxygen species through nicotinamide adenine dinucleotide phosphate oxidase system in vascular smooth muscle cells, which induces smooth muscle cell proliferation and accelerates atherosclerosis [27]. Therefore, UII seems to have a key role in progression of atherosclerotic cardiovascular diseases. Hassan et al. [28] demonstrated UII expression in endothelial cells, foam cells, and myointimal and medial vascular smooth muscle cells of atherosclerotic human coronary arteries.

Higher plasma UII concentrations that were associated with the severity of CAD were demonstrated in patients with stable CAD [29]. Increased UII concentrations have also been demonstrated in hypertension, which could be related to vasoconstrictive and pro-sympathetic effects. Animal studies demonstrated raised blood pressure and heart rate following UII injection which could be inhibited by pentolinium, indicating a direct contribution of the sympathetic nervous system [30, 31]. Another study revealed that intracerebral injection of UII induced elevated sympathetic nerve activity, which was followed by the stimulation of adrenal medulla for secretion of adrenaline [32].

Since UII has pro-atherosclerotic and vasoconstrictive effects especially in coronary resistance arteries, this particular action may have a role in SCF pathogenesis. Maguire and Davenport [33] reported UII expression in endothelial cells of both epicardial coronary arteries and intramyocardial resistance arteries (60–120 μm) but not in cardiac myocytes or vascular smooth muscle cells. Similarly, UII was detected within macrophages of the atherosclerotic plaque but not in vascular smooth muscle cells [34].

Moreover, urotensin receptors, which mediate vasoconstriction, are present in all vascular smooth muscle cells from large epicardial to small resistance arteries [35]. UII may have additional value in ischemia-reperfusion injury and thus aid in SCF phenomenon. In Langendorff, preparations for ischemia–reperfusion injury decrease coronary flow in rats, which is exacerbated by administration of UII during reperfusion [36]. Similarly, in the event of significant endothelial dysfunction, UII may cause vasoconstriction or inadequate vasodilation in coronary arteries with resultant myocardial ischemia [37, 38].

Maguire et al. [34] demonstrated that UII had more pronounced effect on small coronary arteries than epicardial vessels. This enhanced responsiveness may be important in atherosclerotic disorders such as SCF phenomenon.

Study Limitations

Our study has several limitations. First, the study population was relatively small. A larger study population would provide a higher statistical power. The main limitation of our study is the observational nature, which does not explain the exact mechanism of the relationship between increased UII and SCF. In this study, the patients did not undergo intravascular ultrasonography (IVUS) to detect atherosclerotic changes in the coronary arteries. Hence, the coexistence of non-obstructive CAD in patients with "isolated" SCF cannot be established absolutely. Nevertheless, in clinical practice, isolated SCF patients do not undergo IVUS routinely and SCF is usually diagnosed with visual assessment of coronary angiography. Other inflammatory cytokines, except CRP, might be measured to clarify possible causative mediators.

Conclusion

We demonstrated elevated UII levels in patients with SCF and revealed significant association of several atherosclerotic risk factors with SCF. Since UII is a marker of inflammation and atherosclerosis severity, elevated UII may confer an additional risk in this seemingly low-risk condition. Further studies are required to clarify this issue.

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Conflict of interest: The authors declare that they have no conflict of interest.

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