Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp



# Elevated Cystatin C Levels Predict the Incidence of Vasospastic Angina

Akira Funayama, MD; Tetsu Watanabe, MD; Toshiaki Tamabuchi, MD; Yoichiro Otaki, MD; Shunsuke Netsu, MD; Hiromasa Hasegawa, MD; Shintaro Honda, MD; Mitsunori Ishino, MD; Takanori Arimoto, MD; Hiroki Takahashi, MD; Tetsuro Shishido, MD; Takuya Miyamoto, MD; Joji Nitobe, MD; Isao Kubota, MD

***Background:*** Cystatin C, a marker for early stage chronic kidney disease, has been shown to be involved in cardiovascular disease. The relationship between serum cystatin C levels and coronary vasospastic angina (VSA), however, remains to be elucidated. The aim of the present study was to investigate whether elevated cystatin C levels predict the incidence of VSA.

***Methods and Results:*** One hundred and ten patients were referred to hospital due to suspected VSA. VSA was evoked in 59 patients by a vasospasm provocation test with administration of acetylcholine into the coronary arteries. The patients with VSA had lower levels of high-density lipoprotein cholesterol and a higher history of cigarette smoking, higher levels of triglyceride, high-sensitivity C-reactive protein, and higher cystatin C levels compared with those without VSA. There were no differences in serum creatinine or estimated glomerular filtration rate between patients with and without VSA. Multivariate logistic regression indicated that history of smoking (odds ratio, 2.956 $P<0.05$) and cystatin C levels (odds ratio, 2.285; $P<0.01$) were independently associated with the incidence of VSA.

***Conclusions:*** Elevated cystatin C levels were associated with higher incidence of VSA, suggesting that mild renal dysfunction may be implicated in the pathogenesis of coronary artery spasm. (*Circ J* 2011; **75:** 2439–2444)

**Key Words:** Chronic kidney disease; Cystatin C; Vasospastic angina

The incidence of coronary vasospastic angina (VSA) is relatively high in Japanese compared with Caucasian subjects.[1] Coronary vasospasm is associated with the pathogenesis of not only VSA but also acute coronary syndrome.[1,2] The progression of atherosclerosis is one of the key determinants of coronary vasospasm,[3–5] and is accelerated by renal dysfunction.[6] Recently it was reported that early stage chronic kidney disease (CKD) is related to a relatively early stage of atherosclerosis.[7–10]

Cystatin C, a 13-kD basic protein, is a cysteine protease inhibitor involved in the catabolism of proteins. Cystatin C is produced at a constant rate in all nucleated cells and is freely filtered by the glomeruli, without secretion or subsequent reabsorption into the circulation. Thus, serum cystatin C has been shown to be a better endogenous marker of glomerular filtration rate (GFR) than serum creatinine, because serum concentrations are independent of muscle mass and less affected by age or gender.[11–14]

It has been reported that the preclinical state of kidney dysfunction, which can be detected by measurement of serum cystatin C but not serum creatinine or estimated GFR (eGFR), is associated with the development of cardiovascular disease and subsequent mortality.[11,15,16] The relationship between serum cystatin C levels and coronary vasospasm, however, has not been elucidated. The aim of the present study was to investigate whether elevated cystatin C levels predict the incidence of VSA.

## Methods

### Subjects

An angiography-based coronary spasm provocation test was performed on 136 patients who were referred to Yamagata University Hospital due to suspected VSA between June 2008 and October 2010. One hundred and ten patients who had no organic coronary stenosis were enrolled in the study. The ex-

Received January 6, 2011; revised manuscript received May 27, 2011; accepted June 1, 2011; released online July 23, 2011 Time for primary review: 26 days

Department of Cardiology, Pulmonology and Nephrology, Yamagata University School of Medicine, Yamagata, Japan

Names of grants: This study was supported, in part, by a grant-in-aid for Scientific Research (No. 21590923 and 21790700) from the Ministry of Education Culture, Sport, Science and Technology and a grant-in-aid from the Global Century Center of Excellence (COE) program of the Japan Society for the Promotion of Science.

Mailing address: Tetsu Watanabe, MD, Department of Cardiology, Pulmonology and Nephrology, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan. E-mail: tewatana@med.id.yamagata-u.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-11-0008

**Table 1. Subject Clinical Characteristics**

| | VSA group (n=59) | Non-VSA group (n=51) | P value |
|---|---|---|---|
| Age (years) | 64.9±11.2 | 63.2±12.1 | 0.458 |
| Male, n (%) | 41 (69) | 29 (57) | 0.170 |
| BMI (kg/m$^2$) | 24.1±3.2 | 23.2±3.4 | 0.158 |
| Hypertension, n (%) | 39 (66) | 28 (55) | 0.230 |
| Systolic blood pressure (mmHg) | 126.3±16.6 | 127.5±15.0 | 0.686 |
| Diastolic blood pressure (mmHg) | 74.0±11.7 | 73.3±10.5 | 0.757 |
| Diabetes mellitus, n (%) | 7 (12) | 9 (18) | 0.391 |
| Dyslipidemia, n (%) | 31 (53) | 20 (39) | 0.191 |
| Cigarette smoking, n (%) | 35 (59) | 14 (27) | <0.001 |
| Fasting blood glucose (mg/dl) | 104.5±22.9 | 103.7±30.1 | 0.880 |
| $HbA_{1c}$ (%) | 5.63±0.75 | 5.58±0.55 | 0.670 |
| TC (mg/dl) | 177.5±29.7 | 178.6±35.0 | 0.897 |
| HDL-C (mg/dl) | 52.2±12.4 | 60.3±16.4 | 0.005 |
| TG (mg/dl) | 124, 97–176 | 98, 74–133 | 0.002 |
| hs-CRP (mg/dl) | 0.057, 0.032–0.116 | 0.020, 0.015–0.064 | <0.001 |
| Serum creatinine (mg/dl) | 0.77±0.18 | 0.73±0.17 | 0.302 |
| eGFR (ml·min$^{-1}$·1.73 m$^{-2}$) | 75.7±20.8 | 77.4±17.0 | 0.659 |
| Serum cystatin C (ng/ml) | 1.00±0.18 | 0.89±0.14 | <0.001 |
| UACR (mg/g) | 7.00, 4.80–16.2 | 7.40, 6.00–13.3 | 0.275 |
| Prevalence of proteinuria, n (%) | 8 (14) | 6 (12) | 0.808 |
| BNP (pg/dl) | 21.7, 12.1–49.9 | 27.9, 12.0–48.9 | 0.613 |
| Free T3 (pg/ml) | 3.29±0.55 | 3.20±0.47 | 0.358 |
| Free T4 (ng/ml) | 1.06±0.21 | 1.07±0.19 | 0.887 |
| TSH ($\mu$U/ml) | 1.55, 1.21–2.26 | 1.31, 0.74–1.98 | 0.184 |
| LVFF (%) | 68.9±8.5 | 69.1±8.5 | 0.878 |
| Family history of CAD, n (%) | 8 (14) | 8 (16) | 0.752 |
| Aspirin, n (%) | 34 (58) | 24 (47) | 0.268 |
| Nitrates, n (%) | 19 (32) | 7 (14) | 0.024 |
| Statins, n (%) | 24 (41) | 20 (39) | 0.876 |
| Calcium-channel blockers, n (%) | 31 (53) | 16 (31) | 0.025 |
| ACE-I or ARB, n (%) | 21 (36) | 15 (29) | 0.491 |
| $\beta$-blockers, n (%) | 1 (2) | 4 (8) | 0.123 |

Data given as mean±SD, n (%) or median and interquartile range.
VSA, vasospastic angina; BMI, body mass index; $HbA_{1c}$, hemoglobin $A_{1c}$; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio; BNP, B-type natriuretic peptide; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker.

clusion criteria were coronary stenosis (≥50%; n=22), dilated cardiomyopathy (n=1), severe hypertension (>160/110 mmHg; n=1), diabetes mellitus with hyperfiltration (n=1)[17] and malignant disease (n=1). The following coronary risk factors were assessed: hypertension (blood pressure ≥140/90 mmHg or taking anti-hypertensive drugs), history of smoking (≥2 pack years), dyslipidemia (low-density lipoprotein cholesterol ≥140 mg/dl or high-density lipoprotein cholesterol [HDL-C] <40 mg/dl, or taking drugs for dyslipidemia), diabetes mellitus (fasting glucose level ≥126 mg/dl or taking insulin or oral hypoglycemic drugs), body mass index, and previous family history of cardiovascular disease. The study was approved by the institutional ethics committee and all patients gave written informed consent. eGFR was calculated according to the modification of diet in renal disease equation, applying coefficients corrected for the Japanese population based on concentration of serum creatinine [eGFR (ml·min$^{-1}$·1.73 m$^{-2}$)=194×$SCr^{1.094}$×$age^{-0.287}$ (×0.739 if female)].[18] Patients were stratified into 3 CKD stages: stage I, normal eGFR (≥90 ml·min$^{-1}$·1.73 m$^{-2}$); stage II, mild reduction in eGFR (60–89 ml·min$^{-1}$·1.73 m$^{-2}$); and stage III, moderate reduction in eGFR (30–59 ml·min$^{-1}$·1.73 m$^{-2}$). Urine albumin–creatinine ratio (UACR) was calculated by analysis of a single spot urine specimen collected on admission. Proteinuria was defined as UACR ≥30 mg/g.[19]

## Induction of Coronary Spasm

Vasoactive drugs, including calcium channel blockers, nitrates, $\beta$-adrenergic blockers, and other vasodilators were withdrawn for at least 3 days before the study. Before the vasospasm provocation test with acetylcholine, control coronary arteriography was performed. Acetylcholine was then injected from the same angle into the right coronary artery at a dose of 20 $\mu$g or 50 $\mu$g and into the left coronary artery at 50 $\mu$g or 100 $\mu$g each over a period of 20 s. At 3 min from the start of each injection, angiography was performed. In the event of an ischemic change on the electrocardiogram (ECG), or chest pain, angiography was performed at that time. Coronary spasm was defined as total or subtotal occlusion (≥90% stenosis) accompanied by

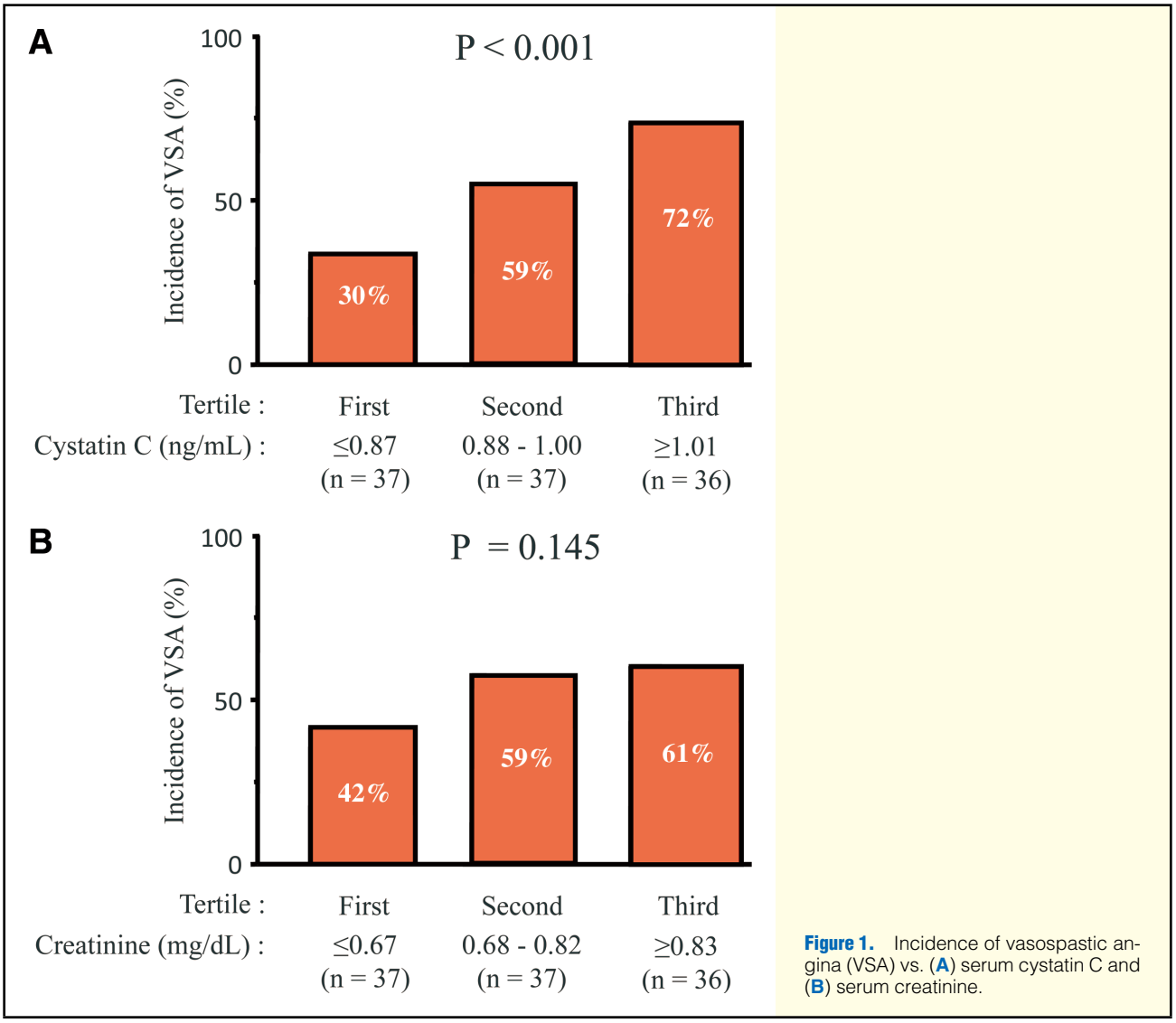


**Figure 1.** Incidence of vasospastic angina (VSA) vs. (**A**) serum cystatin C and (**B**) serum creatinine.

an episode of chest pain, ischemic ST-segment changes on the ECG, or both. The test was discontinued when coronary spasm was induced. Intracoronary infusion of acetylcholine was performed according to a standard method of provocation testing.[20]

### Laboratory Analysis

Blood samples were collected and measured on admission. Serum cystatin C was measured on colloidal gold particle-enhanced colorimetric immunoassay (Nescauto GC Cystatin C, Alfresa Pharma, Osaka, Japan) on a JEOL JCA-BM 8000 series automatic analyzer. General biochemical parameters were measured using routine laboratory methods.

### Statistical Analysis

Results are presented as mean±SD for continuous variables and as percentage of the total number of patients for categorical variables. Skewed data are expressed as median and interquartile range (IQR). Student's unpaired t-test and the chi-square test were used for comparison of continuous and categorical variables, respectively. If the data were not normally distributed, the Mann–Whitney U-test was used. We classified the patients into 3 groups based on cystatin C, creatinine level and CKD stage. Comparison of incidence of VSA among the 3 groups was performed using the Kruskal–Wallis test. Logistic regression analysis was performed to evaluate the relationship between the incidence of coronary vasospasm and the parameters. Only the variables that showed significant associations on univariate analysis were entered into the multivariate analysis. All P-values were 2-sided, and $P<0.05$ were considered significant. Statistical analysis were performed using a standard statistical software package (JMP version 8, SAS Institute, Cary, NC, USA).

## Results

Fifty-nine patients were diagnosed with VSA on coronary spasm provocation with acetylcholine. The clinical characteristics of study patients are listed in Table 1. Serum cystatin C levels were significantly greater in the patients with VSA than in those without VSA (1.00±0.18 ng/ml vs. 0.89±0.14 ng/ml, $P<0.001$). There were no significant differences, however, in serum creatinine concentrations or eGFR between the patients with and without VSA. The prevalence of cigarette smoking

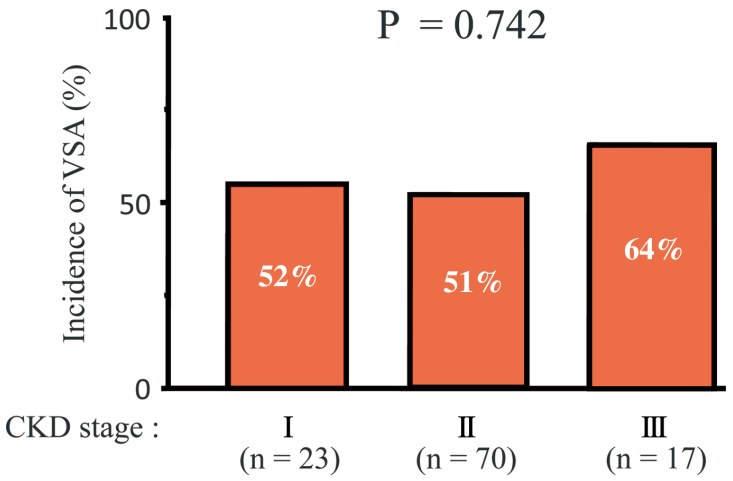


**Figure 2.** Incidence of vasospastic angina (VSA) vs. chronic kidney disease (CKD) stage.

**Table 2. Logistic Regression Analysis for VSA**

| Factor | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95%CI | P value | OR | 95%CI | P value |
| Age* | 1.169 | 0.771–1.786 | 0.536 | | | |
| Male gender | 1.728 | 0.789–3.784 | 0.171 | | | |
| BMI* | 1.330 | 0.895–1.975 | 0.159 | | | |
| Hypertension | 1.602 | 0.741–3.464 | 0.231 | | | |
| Diabetes mellitus | 0.628 | 0.216–1.828 | 0.394 | | | |
| Dyslipidemia | 2.030 | 0.941–4.379 | 0.071 | | | |
| Cigarette smoking | 3.854 | 1.723–8.621 | 0.001 | 2.956 | 1.087–8.040 | 0.034 |
| Family history of CAD | 0.843 | 0.292–2.435 | 0.753 | | | |
| HDL* | 0.553 | 0.358–0.849 | 0.007 | 0.943 | 0.547–1.617 | 0.819 |
| TG* | 2.011 | 1.191–3.370 | 0.011 | 1.843 | 1.000–3.370 | 0.056 |
| LVEF* | 0.967 | 0.654–1.439 | 0.876 | | | |
| BNP* | 0.870 | 0.622–1.335 | 0.617 | | | |
| Serum creatinine* | 1.225 | 0.835–1.797 | 0.301 | | | |
| eGFR* | 0.909 | 0.630–1.328 | 0.656 | | | |
| UACR* | 0.969 | 0.626–1.328 | 0.876 | | | |
| $HbA_{1c}$* | 1.087 | 0.741–1.595 | 0.127 | | | |
| hs-CRP* | 2.059 | 1.035–4.099 | 0.039 | 1.715 | 0.859–3.422 | 0.126 |
| Serum cystatin C* | 2.392 | 1.412–4.050 | 0.001 | 2.285 | 1.268–4.121 | 0.006 |

*Per 1-SD increase.
OR, odds ratio; CI, confidence interval. Other abbreviations see in Table 1.

was significantly higher in the patients with VSA than in those without VSA (59% vs. 27%, P<0.001). High-sensitivity C-reactive protein (hs-CRP) levels were significantly higher in the patients with VSA than in those without VSA (0.057 mg/dl, IQR 0.032–0.116 vs. 0.020 mg/dl, IQR 0.015–0.064, P<0.001). There were no significant differences in prevalence of proteinuria between the patients with and without VSA (14% vs. 12%, P=0.808). All patients were classified into 3 groups according to their serum cystatin C and creatinine levels: cystatin C, ≤0.87 ng/ml (n=37, first tertile); 0.88–1.00 ng/ml (n=37, second tertile); ≥1.01 ng/ml (n=36, third tertile); creatinine, ≤0.67 mg/dl (n=37, first tertile); 0.68–0.82 mg/dl (n=37, second tertile); ≥0.83 mg/dl (n=36, third tertile). The incidence of VSA was highest in patients in the third tertile of cystatin C concentration (Figure 1A), whereas it was not associated with serum creatinine levels (Figure 1B). Next, all patients were classified into 3 groups according to their CKD stage: stage I, eGFR ≥90/ml·min$^{-1}$·1.73 m$^{-2}$ (n=23); stage II, eGFR=60–89/ml·min$^{-1}$·1.73 m$^{-2}$ (n=70); stage III, eGFR=30–59/ml·min$^{-1}$·1.73 m$^{-2}$ (n=17). Although patients in stage III CKD tended to have a greater incidence of VSA compared to those with stage I and II CKD, there were no significant differences among the 3 groups (Figure 2). To assess the factors predicting the incidence of VSA, univariate and multivariate logistic regression analysis was performed (Table 2). On univariate analysis, the history of cigarette smoking, HDL-C, triglyceride levels, hs-CRP levels and cystatin C levels were associated with the incidence of VSA. Multivariate analysis showed that the history of cigarette smoking and cystatin C levels were independent predictors of the incidence of VSA.

## Discussion

The present study has demonstrated that elevated serum cys-

tatin C levels may predict the incidence of VSA. The history of smoking and hs-CRP levels were also higher in patients with VSA than in those without VSA, which is consistent with the results of previous studies.[21]

It has been reported that the progression of atherosclerosis is one of the key determinants of coronary artery spasm.[3,22] Renal dysfunction was shown to cause vascular damage and progression of atherosclerosis,[7–9] and even mild renal dysfunction may result in the progression of atherosclerosis and deterioration in cardiovascular outcomes.[23] Recently, lower levels of eGFR have been postulated to be associated with high prevalence of VSA,[24] but there have been few studies demonstrating a relationship between the incidence of VSA and mild renal dysfunction. To our knowledge, this is the first report to indicate that subtle renal dysfunction may be implicated in the pathogenesis of coronary vasospasm.

In general, renal function is evaluated by measurement of serum creatinine levels or by creatinine-based eGFR. Serum creatinine levels, however, are influenced by many factors, including muscle mass, age and gender.[25] Recently, cystatin C has gained attention as a promising marker of renal function. Serum cystatin C levels have been shown to reflect eGFR, as measured by inulin clearance, more precisely than serum creatinine levels, because serum cystatin C concentrations are independent of muscle mass and less affected by age or gender.[11–14] Previous reports have indicated that serum cystatin C concentrations can be used to detect mild to moderate decreases in eGFR that are not evident from measurement of serum creatinine levels.[11] In the present study, elevated serum cystatin C levels were associated with the incidence of VSA, whereas the incidence of VSA was not associated with serum creatinine levels (**Figure 1**). These results suggest that subtle decreases in eGFR, which can be detected by measurement of cystatin C but not creatinine, may be implicated in the incidence of VSA. Although it has been reported that the concentration of serum cystatin C is affected by thyroid function,[12] there was no difference in thyroid function between the patients with and without VSA in the present study (**Table 1**).

The relationship between mild renal dysfunction and incidence of VSA may be explained by several cooperating mechanisms. Mild renal dysfunction has been shown to promote atherosclerosis and vascular damage by causing high blood pressure, dyslipidemia, vascular inflammation, and oxidative stress.[26–28] It has also been reported that dyslipidemia, current smoking, chronic low-grade inflammation, and oxidative stress are involved in the pathogenesis of coronary vasospasm.[21,29–31]

Previous studies have demonstrated that endothelial dysfunction is involved in the pathogenesis of coronary spasm and that endothelial nitric oxide (NO) activity is reduced in spastic coronary arteries.[32,33] Impaired release of endothelium-derived relaxing factor as a result of endothelial dysfunction has been demonstrated in atherosclerotic coronary arteries, suggesting that endothelial dysfunction plays a causal role in coronary spasm.[32] A recent report indicated that renal dysfunction suppresses endothelial NO synthetase activity, and causes the development of atherothrombosis.[34] These results suggest that renal dysfunction may be implicated in the incidence of coronary vasospasm through endothelial dysfunction.

Recently it was reported that statins can suppress VSA by improving endothelial function, enhancing NO activity, and suppressing inflammation and $Ca^{2+}$ sensitivity of coronary smooth muscle.[35] There was no significant difference in use of statins between the patients with and without VSA in the present study.

Although low-grade inflammation may play an important role in pathogenesis of VSA,[21] we did not find significant positive correlations between serum cystatin C and hs-CRP levels in patients with VSA. It remains unclear whether serum cystatin C directly influences inflammatory response. We did not evaluate the levels of other inflammatory cytokines in the present study group.

There was a small number of stage III CKD patients enrolled in the present study. Therefore, further studies including a large number of CKD patients are needed to investigate the relationship between CKD stage, prevalence of proteinuria and incidence of VSA.

In conclusion, elevated serum cystatin C levels were significantly associated with the incidence of coronary spasm, suggesting that even subtle renal dysfunction, which cannot be detected via serum creatinine levels, is associated with the incidence of VSA. Elevated cystatin C level may be a useful marker for the incidence of VSA.

## Acknowledgments

This study was supported, in part, by a grant-in-aid for Scientific Research (No. 21590923 and 21790700) from the Ministry of Education Culture, Sport, Science and Technology and a grant-in-aid from the Global Century Center of Excellence (COE) program of the Japan Society for the Promotion of Science.

## References

1. Yasue H, Kugiyama K. Coronary spasm: Clinical features and pathogenesis. *Intern Med* 1997; **36:** 760–765.
2. Pristipino C, Beltrame JF, Finocchiaro ML, Hattori R, Fujita M, Mongiardo R, et al. Major racial differences in coronary constrictor response between Japanese and Caucasians with recent myocardial infarction. *Circulation* 2000; **101:** 1102–1108.
3. Nakagawa H, Morikawa Y, Mizuno Y, Harada E, Ito T, Matsui K, et al. Coronary spasm preferentially occurs at branch points: An angiographic comparison with atherosclerotic plaque. *Circ Cardiovasc Interv* 2009; **2:** 97–104.
4. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation* 2005; **111:** 3481–3488.
5. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; **352:** 1685–1695.
6. El Nahas M. Cardio-kidney-damage: A unifying concept. *Kidney Int* 2010; **78:** 14–18.
7. Cerne D, Kaplan-Pavlovcic S, Kranjec I, Jurgens G. Mildly elevated serum creatinine concentration correlates with the extent of coronary atherosclerosis. *Ren Fail* 2000; **22:** 799–808.
8. Zhang L, Zhao F, Yang Y, Qi L, Zhang B, Wang F, et al. Association between carotid artery intima-media thickness and early-stage CKD in a Chinese population. *Am J Kidney Dis* 2007; **49:** 786–792.
9. Kawamoto R, Ohtsuka N, Kusunoki T, Yorimitsu N. An association between the estimated glomerular filtration rate and carotid atherosclerosis. *Intern Med* 2008; **47:** 391–398.
10. Desbien AM, Chonchol M, Gnahn H, Sander D. Kidney function and progression of carotid intima-media thickness in a community study. *Am J Kidney Dis* 2008; **51:** 584–593.
11. Shlipak MG, Katz R, Sarnak MJ, Fried LF, Newman AB, Stehman-Breen C, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med* 2006; **145:** 237–246.
12. Kiyosue A, Hirata Y, Ando J, Fujita H, Morita T, Takahashi M, et al. Plasma cystatin C concentration reflects the severity of coronary artery disease in patients without chronic kidney disease. *Circ J* 2010; **74:** 2441–2447.
13. Iwanaga Y, Miyazaki S. Cystatin C in a high-risk combination. *Circ J* 2009; **73:** 1593–1594.
14. Arimoto T, Takeishi Y, Niizeki T, Takabatake N, Okuyama H, Fukui A, et al. Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. *J Card Fail* 2005; **11:** 595–601.
15. Muntner P, Mann D, Winston J, Bansilal S, Farkouh ME. Serum cystatin C and increased coronary heart disease prevalence in US adults without chronic kidney disease. *Am J Cardiol* 2008; **102:** 54–57.
16. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB,

et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005; **352:** 2049–2060.
17. Jin Y, Moriya T, Tanaka K, Matsubara M, Fujita Y. Glomerular hyperfiltration in non-proteinuric and non-hypertensive Japanese type 2 diabetic patients. *Diabetes Res Clin Pract* 2006; **71:** 264–271.
18. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53:** 982–992.
19. Konta T, Hao Z, Abiko H, Ishikawa M, Takahashi T, Ikeda A, et al. Prevalence and risk factor analysis of microalbuminuria in Japanese general population: The Takahata study. *Kidney Int* 2006; **70:** 751–756.
20. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008): Digest version. *Circ J* 2010; **74:** 1745–1762.
21. Itoh T, Mizuno Y, Harada E, Yoshimura M, Ogawa H, Yasue H. Coronary spasm is associated with chronic low-grade inflammation. *Circ J* 2007; **71:** 1074–1078.
22. Miyao Y, Kugiyama K, Kawano H, Motoyama T, Ogawa H, Yoshimura M, et al. Diffuse intimal thickening of coronary arteries in patients with coronary spastic angina. *J Am Coll Cardiol* 2000; **36:** 432–437.
23. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 2001; **134:** 629–636.
24. Koga S, Ikeda S, Nakata T, Yasunaga T, Takeno M, Koide Y, et al. Low glomerular filtration rate is associated with high prevalence of vasospastic angina. *Circ J* 2011; **75:** 1691–1695.
25. Hsu CY, Chertow GM, Curhan GC. Methodological issues in studying the epidemiology of mild to moderate chronic renal insufficiency. *Kidney Int* 2002; **61:** 1567–1576.
26. Hallan S, de Mutsert R, Carlsen S, Dekker FW, Aasarød K, Holmen J. Obesity, smoking, and physical inactivity as risk factors for CKD: Are men more vulnerable? *Am J Kidney Dis* 2006; **47:** 396–405.
27. Tsuchikura S, Shoji T, Shimomura N, Kakiya R, Emoto M, Koyama H, et al. Serum C-reactive protein and thioredoxin levels in subjects with mildly reduced glomerular filtration rate. *BMC Nephrol* 2010; **11:** 7.
28. Vaziri ND, Navab M, Fogelman AM. HDL metabolism and activity in chronic kidney disease. *Nat Rev Nephrol* 2010; **6:** 287–296.
29. Yamagishi M, Ito K, Tsutsui H, Miyazaki S, Goto Y, Nagaya N, et al. Lesion severity and hypercholesterolemia determine long-term prognosis of vasospastic angina treated with calcium channel antagonists. *Circ J* 2003; **67:** 1029–1035.
30. Miwa K, Fujita M, Miyagi Y, Inoue H, Sasayama S. High-density lipoprotein cholesterol level and smoking modify the prognosis of patients with coronary vasospasm. *Clin Cardiol* 1995; **18:** 267–272.
31. Miyamoto S, Kawano H, Sakamoto T, Soejima H, Kajiwara I, Hokamaki J, et al. Increased plasma levels of thioredoxin in patients with coronary spastic angina. *Antioxid Redox Signal* 2004; **6:** 75–80.
32. Kugiyama K, Yasue H, Okumura K, Ogawa H, Fujimoto K, Nakao K, et al. Nitric oxide activity is deficient in spasm arteries of patients with coronary spastic angina. *Circulation* 1996; **94:** 266–271.
33. Kugiyama K, Ohgushi M, Motoyama T, Sugiyama S, Ogawa H, Yoshimura M, et al. Nitric oxide-mediated flow-dependent dilation is impaired in coronary arteries in patients with coronary spastic angina. *J Am Coll Cardiol* 1997; **30:** 920–926.
34. Yilmaz MI, Saglam M, Caglar K, Cakir E, Sonmez A, Ozgurtas T, et al. The determinants of endothelial dysfunction in CKD: Oxidative stress and asymmetric dimethylarginine. *Am J Kidney Dis* 2006; **47:** 42–50.
35. Yasue H, Mizuno Y, Harada E, Itoh T, Nakagawa H, Nakayama M, et al. Effects of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, fluvastatin, on coronary spasm after withdrawal of calcium-channel blockers. *J Am Coll Cardiol* 2008; **51:** 1742–1748.