



## Low Glomerular Filtration Rate Is Associated With High Prevalence of Vasospastic Angina

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**Background:** Although chronic kidney disease is associated with a high prevalence of cardiovascular disease, the relationship between coronary artery spasm and renal dysfunction has not been elucidated.

**Methods and Results:** We evaluated 139 patients with chest pain at rest who had no significant organic stenosis on coronary angiograms and who underwent coronary spasm provocation tests using acetylcholine or ergonovine. The results of the provocation tests revealed that 59 patients had vasospastic angina (VSA), and that 80 did not (non-VSA). We analyzed the association between VSA and renal dysfunction using the estimated glomerular filtration rate (eGFR). The eGFR was significantly lower in the VSA group than in the non-VSA group ( $P=0.013$ ). The patients were assigned to quartiles (Q) 1, 2, 3 and 4 based on eGFR ( $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ )  $<64.1$ ,  $64.1-74.7$ ,  $74.8-85.0$  and  $\geq 85.1$ , respectively, in each of which the prevalence of VSA was 57%, 53%, 34% and 26%, respectively. The prevalence of VSA was significantly higher in Q1 than in Q4 ( $P=0.008$ ). Logistic regression analysis showed that the independent factors associated with the presence of VSA were a lower eGFR ( $P=0.011$ ) and male gender ( $P=0.001$ ).

**Conclusions:** Lower levels of eGFR in our study population were significantly and independently associated with a high prevalence of VSA, suggesting that a lower eGFR could be a risk factor for VSA. (*Circ J* 2011; **75**: 1691–1695)

**Key Words:** Chronic kidney disease; Coronary spasm; Endothelial dysfunction

Renal dysfunction is associated with a higher frequency of cardiovascular disease, especially among patients with advanced or end-stage renal disease. The incidence of cardiovascular events has recently increased among patients with even mild renal dysfunction.<sup>1,2</sup> Coronary artery disease, including acute coronary syndrome, is considered to be the most common type of cardiovascular event arising in patients with chronic kidney disease (CKD).<sup>3-7</sup> However, which types of cardiovascular events are more frequent in CKD patients have not yet been established and the mechanisms of the association between renal dysfunction and the high frequency of cardiovascular events remain unclear.

Coronary artery spasm plays an important role in the pathogenesis of angina, acute myocardial infarction, arrhythmia and sudden death, particularly in Japan.<sup>8-12</sup> The precise underlying mechanism of coronary spasm remains unknown, but endothelial dysfunction is probably involved, and its key determinant is reduced endothelial-derived nitric oxide (NO) activity.<sup>13</sup> Endothelial dysfunction is also a feature of CKD

and it might contribute to the high prevalence of atherosclerosis and cardiovascular disease in such patients.<sup>14-16</sup> Thus, endothelial dysfunction is an important underlying factor for both of these pathologies, but their interactions have not been elucidated. The present study investigates the relationship between renal dysfunction assessed by estimated glomerular filtration rates (eGFR) and vasospastic angina (VSA).

### Methods

#### Study Group

We retrospectively evaluated 139 consecutive patients who were admitted to hospital with chest pain at rest suggestive of VSA, and who underwent diagnostic coronary angiography and coronary spasm provocation tests between August 2001 and December 2008. We defined VSA as episodes of spontaneous chest symptoms at rest associated with transient ST segment changes on 12-lead or ambulatory ECG, as well as angiographically documented coronary spasm after provoca-

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**Table 1. Patients' Characteristics**

	Non-VSA (n=80)	VSA (n=59)	P value
Age (years)	59±13	62±10	0.15
Male	34 (43%)	43 (73%)	0.001
Hypertension	35 (44%)	23 (39%)	0.57
Dyslipidemia	26 (33%)	28 (48%)	0.074
DM	12 (15%)	12 (20%)	0.41
Smoking history			0.003
Never	53 (66%)	22 (37%)	
Current smoker	18 (23%)	23 (39%)	
Ex-smoker	9 (11%)	14 (24%)	
Obesity	24 (30%)	19 (33%)	0.73
Medications			
CCB	11 (14%)	12 (20%)	0.30
ACE inhibitors	3 (4%)	1 (2%)	0.64
ARB	15 (19%)	12 (20%)	0.82
$\beta$ -blockers	3 (4%)	0	0.26
Nitrates	3 (4%)	2 (3%)	1.00
Statins	14 (18%)	19 (32%)	0.044
Proteinuria			0.35
Negative	75 (94%)	55 (93%)	
Trace	3 (4%)	4 (7%)	
1+	2 (3%)	0 (0%)	
2+ or higher	0 (0%)	0 (0%)	

VSA, vasospastic angina; DM, diabetes mellitus; CCB, calcium-channel blockers; ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blockers.

tion with either acetylcholine or ergonovine. Based on this definition, 59 patients were diagnosed with VSA and the 80 without signs of coronary spasm were referred to as non-VSA. All patients provided written informed consent to undergo coronary angiography and the coronary spasm provocation test.

### Coronary Angiography and Provocation Test

Antianginal and antihypertensive drugs, including calcium-channel blockers, nitrates,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers, were not administered for at least 2 days before coronary angiography, unless such withdrawal was considered hazardous for the patient. Baseline coronary angiography was performed using 4- or 5-Fr Judkins catheters without premedication such as an intracoronary injection of isosorbide dinitrate. When coronary angiography did not indicate significant organic coronary stenosis ( $>25\%$  stenosis of the luminal diameter), the coronary spasm provocation test was applied using acetylcholine or ergonovine according to operator preference. A temporary pacing lead was inserted into the right ventricular apex through the right femoral vein before provocation using acetylcholine, because severe bradycardia can develop. Incremental doses of acetylcholine were injected into the coronary arteries over a period of 20 s (left coronary artery, 20, 50 and 100  $\mu$ g; right coronary artery, 20 and 50  $\mu$ g). Ergonovine was injected incrementally into the coronary arteries over a period of 2 min (left coronary artery, 20, 40 and 60  $\mu$ g; right coronary artery, 20 and 40  $\mu$ g). The patients were examined by coronary angiography at 2 min after each injection, or when ST segment changes or chest pain, or both, appeared. Coronary artery spasm was defined as angiographically total or subtotal ( $>90\%$ ) occlusion of the epicardial

coronary arteries with signs of myocardial ischemia such as chest pain or ST segment elevation or depression on ECG after provocation.<sup>17</sup>

### Study Variables

We calculated the eGFR from age and serum creatinine (Scr) using the Japanese GFR estimation equation proposed by the Japanese Society of Nephrology as follows:<sup>18</sup>  $\text{eGFR (ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}) = 194 \times \text{age}^{-0.287} \times \text{Scr}^{-1.094}$  (if female,  $\times 0.739$ ). We grouped the patients by eGFR quartiles to compare the prevalence of VSA associated with eGFR. Proteinuria was evaluated by urine dipstick testing and the results are expressed as negative, trace, 1+ and 2+ or higher.

We also assessed coronary risk factors, including a history of smoking, hypertension, dyslipidemia, diabetes mellitus and obesity. Smoking history was divided into 3 categories of never, current, and ex-smoker. Ex-smoker was defined as previous smoker who had quit smoking for more than 6 months. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg, and/or under antihypertensive treatment. Diabetes mellitus was defined as fasting plasma glucose  $\geq 126$  mg/dl, postprandial blood glucose  $\geq 200$  mg/dl, and/or under glucose-lowering treatment. Dyslipidemia was defined as total cholesterol  $\geq 220$  mg/dl, low-density lipoprotein cholesterol  $\geq 140$  mg/dl, high-density lipoprotein cholesterol  $< 40$  mg/dl, fasting triglycerides  $\geq 150$  mg/dl or under lipid-lowering treatment. We defined body mass index (BMI) as weight (kg) divided by the square of the height (m), and obesity as BMI  $\geq 25$  kg/m<sup>2</sup>.

### Statistical Analysis

Results are expressed as means  $\pm$  standard deviation or as numbers and ratios (%). Continuous variables were compared using an unpaired t-test and categorical variables were compared using the  $\chi^2$  test and Fisher's exact test. Significant factors related to the presence of VSA were determined using a multivariable logistic regression model. Factors with a P-value  $< 0.10$  in the univariate were entered into the multivariate model. Data were analyzed using SPSS 11.0 statistical software (SPSS, Inc, Chicago, IL, USA). A P-value  $< 0.05$  was considered statistically significant. Bonferroni's adjustment was applied to multiple comparisons among eGFR quartiles.

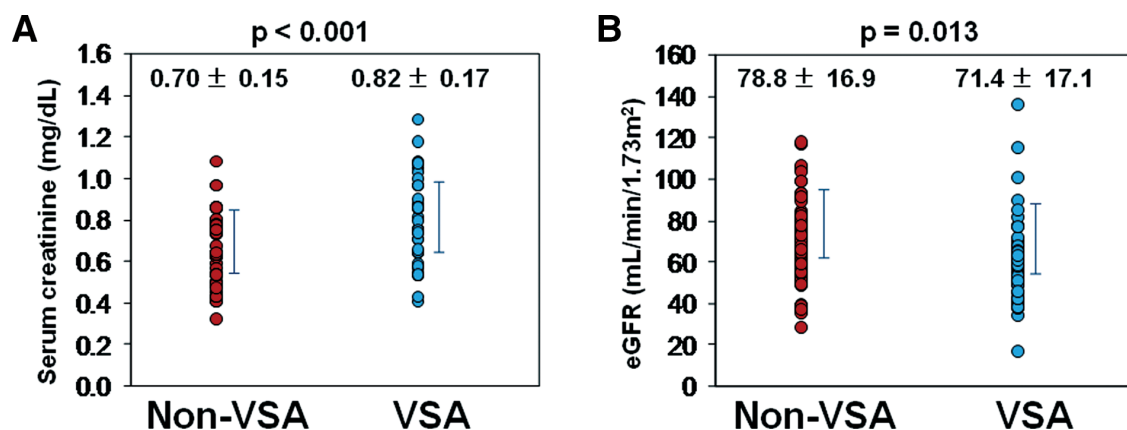
## Results

### Patients' Characteristics

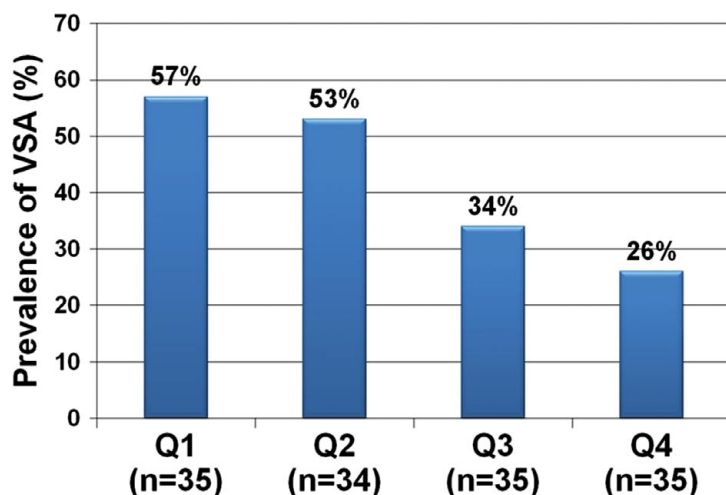
**Table 1** lists the clinical characteristics of the patients in the present study. Age, prevalence of hypertension, dyslipidemia, diabetes mellitus, obesity, and level of proteinuria determined by urinalysis did not significantly differ between the VSA and non-VSA groups. Compared with the non-VSA group, the VSA group contained a significantly higher proportion of males ( $P=0.001$ ) and those with a history of smoking ( $P=0.003$ ). The proportion of statin use was higher in the VSA group than in the non-VSA group ( $P=0.044$ ), but the frequencies of using other drugs were similar between the groups.

### Comparison of Scr and eGFR

The Scr level and eGFR were compared between the VSA and non-VSA groups (**Figure 1**). Scr was significantly higher ( $0.82 \pm 0.17$  vs.  $0.70 \pm 0.15$  mg/dl,  $P<0.001$ ) and eGFR was significantly lower ( $71.4 \pm 17.1$  vs.  $78.8 \pm 16.9$  ml  $\cdot$  min<sup>-1</sup>  $\cdot$  1.73 m<sup>-2</sup>,  $P=0.013$ ) in the VSA group than in the non-VSA group.



**Figure 1.** Comparison of serum creatinine (A) and eGFR (B) values between the VSA and non-VSA groups. Serum creatinine was significantly higher ( $P<0.001$ ) and eGFR was significantly lower ( $P=0.013$ ) in the VSA group than in the non-VSA group. eGFR, estimated glomerular filtration rate; VSA, vasospastic angina.



**Figure 2.** Relationship between eGFR quartiles and prevalence of VSA. Quartiles (Q) of eGFR ( $\text{mL} \cdot \text{min}^{-1} \cdot 1.73 \text{m}^{-2}$ ) were Q1 ( $<64.1$ ), Q2 (64.1–74.7), Q3 (74.8–85.0), and Q4 ( $\geq 85.1$ ). Prevalence of VSA is significantly higher in Q1 than in Q4 ( $P=0.008$ ). eGFR, estimated glomerular filtration rate; VSA, vasospastic angina.

	Univariate			Multivariate		
	OR	95%CI	P value	OR	95%CI	P value
Age	1.02	0.99–1.05	0.15			
Male	3.64	1.76–7.51	<0.001	4.45	1.92–10.34	0.001
Hypertension	0.82	0.41–1.63	0.57			
Dyslipidemia	1.88	0.94–3.75	0.075	2.24	0.99–5.09	0.053
DM	1.45	0.60–3.50	0.41			
Obesity	1.14	0.55–2.35	0.73			
Current smoker	2.20	1.05–4.62	0.037	1.95	0.82–4.63	0.13
eGFR	0.97	0.95–0.99	0.016	0.97	0.94–0.99	0.011

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate. Other abbreviations see in Table 1.

### Comparison of Prevalence of VSA Among eGFR Quartiles

**Figure 2** shows the prevalence of VSA stratified by eGFR quartiles (Q) 1, 2, 3 and 4 ( $<64.1$ , 64.1–74.7, 74.8–85.0 and  $\geq 85.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{m}^{-2}$ , respectively), with Q4 being the reference group. The prevalence of VSA was significantly

higher in Q1 than in Q4 (57% vs. 26%,  $P=0.008$ ). The prevalence of VSA tended to be higher in Q2 than in Q4 (53% vs. 26%), but the difference did not reach significance. The prevalence of VSA was similar in Q3 and Q4 (34% vs. 26%).

### Logistic Regression Analysis of the Presence of VSA

Univariate logistic regression analysis revealed that the presence of VSA was significantly associated with male gender, being a current smoker and eGFR (Table 2), but not with age, hypertension, diabetes mellitus, or obesity. Multivariate logistic regression analysis revealed that independent factors associated with the presence of VSA were eGFR (odds ratio (OR) 0.97, 95% confidence interval (CI) 0.94–0.99,  $P=0.011$ ) and male gender (OR 4.45, 95%CI 1.92–10.34,  $P=0.001$ ) (Table 2).

### Discussion

In the present study, the level of Scr was significantly higher and the level of eGFR was significantly lower in the VSA group than in the non-VSA group. Patients with lower eGFR levels, especially  $<64.1 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , were more likely to have a high prevalence of VSA. Multivariate analysis showed that eGFR and male gender were independently associated with the presence of VSA.

Several proposed mechanisms can explain VSA. An altered contractile response of coronary smooth muscle and impaired endothelial function, especially NO function, is associated with VSA,<sup>19</sup> and endothelial NO activity is reduced in the spastic coronary arteries of such patients.<sup>13,20</sup> Furthermore, chronic inflammation and oxidative stress can affect these process and cause coronary artery spasm.<sup>19,21,22</sup>

The present findings showed that male gender and a lower eGFR were independently associated with the presence of VSA. The association with male gender agrees with previous findings.<sup>21</sup> The association between male gender and coronary artery spasm might be accounted for as follows. Several studies have suggested sex differences in vascular reactivity. Celermajer et al found greater flow-mediated vasodilation of the brachial artery in premenopausal women than in similarly aged men.<sup>23</sup> Majmudar et al found a greater vasoconstrictive response to a NO synthase inhibitor (L-NG-monomethyl-arginine: L-NMMA) in premenopausal women than in age-matched men.<sup>24</sup> This finding suggests that men produce less basal NO than women. The possibility that testosterone influences endothelium-dependent vasodilation has been investigated. Herman et al examined endothelium-dependent vasodilation of the brachial artery in atherosclerosis-free men undergoing androgen deprivation to treat prostate cancer.<sup>25</sup> Androgens inhibited the endogenous generation of NO and thus mitigated endothelium-dependent vasodilation.

On the other hand, few studies have evaluated the association between VSA and eGFR. The influence of kidney dysfunction on coronary artery spasm might be explained by the following mechanisms. CKD is associated with endothelial dysfunction mediated by reduced NO bioavailability, in which asymmetric dimethylarginine (ADMA) plays an important role. ADMA, an endogenous NO synthase inhibitor, is related to the development of endothelial dysfunction in various diseases.<sup>26</sup> Many tissues, such as the heart, endothelium and smooth muscle cells, potentially synthesize ADMA via arginine methyltransferase, and then ADMA is metabolized mainly by dimethylarginine dimethylaminohydrolase and partly eliminated by urinary excretion.<sup>27</sup> In particular, levels of ADMA are inversely related to eGFR in patients with CKD.<sup>28</sup> In a canine model of CKD, the downregulation of dimethylarginine dimethylaminohydrolase-II and endothelial NO synthase lead to blunted coronary vasodilation induced by acetylcholine.<sup>15</sup> Furthermore, CKD is associated with elevated inflammatory factors, hyperhomocysteinemia, oxidant stress, and

an activated rennin–angiotensin system,<sup>27,29,30</sup> which also can lead to endothelial dysfunction. Thus, CKD might be associated with the presence of VSA through endothelial dysfunction caused by these mechanisms. Further studies are required to determine whether and how interactions among these factors increase the risk of coronary artery spasm. Moreover, which types of patients with CKD are likely to develop either obstructive coronary artery disease or VSA should be clarified.

Smoking could be a source of free radicals and thus cause coronary artery spasm by decreasing NO activity; it is also considered a major risk factor for VSA.<sup>19,31</sup> We found a higher proportion of a smoking history among patients with than without VSA. However, multivariate logistic regression analysis showed that current smoking was not significantly associated with the presence of VSA, although only 39% and 23% of the VSA and non-VSA groups, respectively, currently smoked. Thus, the relatively low proportion of patients with a history of smoking among our cohort might have been responsible for the lower association between VSA and smoking in the present study.

### Study Limitations

Being a retrospective single-center analysis of a small cohort is the major limitation of the present study. Although microalbuminuria correlates with impaired endothelial function,<sup>32</sup> we did not measure urinary albumin. Therefore, the possibility that some patients with a normal eGFR already had subclinical renal damage cannot be excluded. Moreover, we did not measure surrogate markers related to endothelial function including NO, ADMA, high-sensitive CRP and oxidative stress. We did not apply the spasm provocation test to patients with significant organic coronary stenosis to avoid the possibility of inducing coronary spasm severe enough to elicit critical adverse reactions, including cardiogenic shock and fatal ventricular arrhythmia. Consequently, our results can be applied only to patients without significant coronary stenosis. In addition, patients with advanced or endstage kidney dysfunction or those on predialysis did not undergo angiography because of the high risk for contrast-induced nephropathy. Thus, our findings were generated from a limited population with a very mild reduction in eGFR, and could not be demonstrated in patients with an advanced reduction in eGFR.

### Conclusions

Lower levels of eGFR were significantly and independently associated with a high prevalence of VSA in a limited population of patients with chest pain at rest and without significant organic coronary stenosis or an advanced reduction in eGFR. Thus, a lower eGFR might be a risk factor for VSA.

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