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Gender Differences Among Korean Patients With Coronary Spasm

Ju Hwan Lee, MD¹, Hyunsang Lee, MD¹, Myung Hwan Bae, MD², Yong Seop Kwon, MD³, Jang Hoon Lee, MD², Hyeon Min Ryu, MD², Yongwhi Park, MD⁴, Dong Heon Yang, MD², Hun Sik Park, MD², Yongkeun Cho, MD², Shung Chull Chae, MD², Jae-Eun Jun, MD² and Wee-Hyun Park, MD²

¹Department of Internal Medicine, CHA University, CHA Gumi Medical Center, Gumi,

²Department of Internal Medicine, Kyungpook National University Hospital, Daegu,

³Department of Internal Medicine, Busan St. Mary's Medical Center, Busan,

⁴Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Korea

ABSTRACT

Background and Objectives: The gender differences among Korean patients with coronary spasm have not been defined. We thus determined the gender differences among Korean patients with coronary spasm. **Subjects and Methods:** Patients with chest pain and/or syncope who were admitted to Kyungpook National University Hospital between January 2001 and August 2008 were included. Provocation of coronary vasospasm with intracoronary ergonovine maleate was performed when baseline coronary angiography showed no significant stenosis or there was a strong clinical suspicion of coronary spasm. The clinical characteristics were analyzed from 104 consecutive patients (56 ± 9 years of age; 21 females) who were diagnosed with coronary spasm. **Results:** Female patients were younger (52 ± 7 vs. 57 ± 10 years, p=0.046) with lower rates of smoking and alcohol consumption histories than male patients (19% vs. 65%, p<0.001; and 43% vs. 89%, p<0.001, respectively). The other clinical characteristics were not significantly different, except for the triglyceride levels. **Conclusion:** The majority of patients with coronary spasm were males who were smokers and alcohol consumers. The female patients had lower rates of smoking and alcohol consumption, and they were younger than the male patients. Further studies are needed to investigate the relevance of gender differences in the pathogenesis of coronary spasm. (*Korean Circ J* 2009;39:423-427)

KEY WORDS: Coronary vasospasm; Sex differences.

Introduction

Coronary spasm causes atypical chest pain, syncope, myocardial infarction, and even sudden cardiac death.^{1,2)} Previous studies have shown that coronary spasm is common in the Orient, especially in the Far East, and it is closely related to cigarette smoking.³⁻¹⁰⁾ According to a recent study, coronary spasm has been documented in nearly 50% of patients with suspected acute coronary

syndrome.¹¹⁾ In Korea, many studies have been performed on coronary spasm. According to a previous Korean study, patients with coronary spasm have a higher prevalence among male and younger patients as compared to patients with obstructive coronary artery disease, and smoking appears to be the most important risk factor for coronary spasm.¹²⁾ However, because the clinical characteristics of Korean female patients with coronary spasm have not been clearly defined, we determined the gender differences among Korean patients with coronary spasm.

Subjects and Methods

Patients

Patients with chest pain and/or syncope admitted to the Kyungpook National University Hospital between January 2001 and August 2008 were included in this study. Provocation of coronary vasospasm was performed when baseline coronary angiography showed no significant stenosis and/or there was strong clinical suspicion

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Correspondence: Yongkeun Cho, MD, Department of Internal Medicine, Kyungpook National University Hospital, 200 Dongdeok-ro, Jung-gu, Daegu 700-721, Korea

Tel: 82-53-420-5528, Fax: 82-53-426-2046

E-mail: choyk@mail.knu.ac.kr

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of coronary spasm, such as resting chest pain relieved by sublingual nitroglycerin. Patients with a history of myocardial infarction or coronary intervention were excluded from further analysis. One hundred four consecutive patients were diagnosed with coronary spasm and included in this study. The clinical characteristics of patients, such as age, body mass index (BMI), symptoms, lipid levels, and prevalence of hypertension, cigarette smoking, alcohol consumption, and diabetes were analyzed. The levels of inflammatory markers, such as high sensitivity-C reactive protein (hs-CRP) were also determined.

Provocation test

Coronary angiography was performed with the Judkins technique before noon. No medication had been taken for at least 24 hours before coronary angiography, except for sublingual nitroglycerin. Significant organic stenosis was defined as $\geq 50\%$ luminal narrowing that did not respond to intracoronary nitrate infusion. Ergonovine maleate (0.2 mg/mL; Jeil Pharmaceutical, Dae-gu, Korea) in saline solution was first injected into the right coronary artery in incremental doses of 20, 30, and 50 μ g, and then into the left coronary artery in a similar manner at 3-minute intervals. Coronary angio-

graphy was performed when there were ST-segment changes or development of chest pain within 1 minute after each ergonovine injection. When coronary spasm was provoked and did not spontaneously resolve, 0.2-0.5 mg of nitroglycerin was administered into the coronary artery. Positive results were defined as focal or diffuse transient $\geq 95\%$ luminal narrowing accompanied by typical chest pain and/or ST-T changes in the electrocardiogram (ECG). Focal spasm was defined as transient discrete luminal narrowing; diffuse spasm was defined as luminal narrowing from proximal-to-distal in three major epicardial coronary arteries. Proximal spasm was defined as that of segments 1, 2, 5, 6, and 11, and distal spasm was defined as that of segments 3, 4, 7, 8, 9, 12, 13, 14, and 15 of the American Heart Association classification.¹³⁾ Multivessel coronary artery spasm was defined as spasm of ≥ 2 major epicardial coronary arteries. Catheter-induced spasms were excluded. Before the procedure, coronary angiography and the provocation test were explained to all patients and written informed consent was obtained from every patient.

Statistical analysis

Values are expressed as the mean \pm standard deviation.

Table 1. Clinical characteristics

	Male (n=83)	Female (n=21)	p
Age (years)	57 \pm 10 (31-78)	52 \pm 7 (41-66)	0.046
Initial presentation (%)			0.517
Chest pain	76 (92)	18 (86)	
ST-elevation myocardial infarction	3 (4)	0	0.941
Non-ST elevation myocardial infarction	5 (6)	2 (9)	0.941
Syncope	4 (5)	2 (10)	
Chest pain and syncope	3 (4)	1 (5)	
Diabetes (%)	12 (14)	0	0.119
Hypertension (%)	35 (42)	7 (33)	0.620
Current smoking (%)	54 (65)	4 (19)	<0.001
Smoking including ex-smoking (%)	69 (83)	4 (19)	<0.001
Smoking including passive and ex-smoking (%)	69 (83)	7 (33)	<0.001
Family history of coronary artery disease (%)	8 (10)	5 (24)	0.131
Alcohol (%)			<0.001
Abstainer	9 (10.8)	12 (57.1)	
Light drinker	33 (39.8)	7 (33.3)	
Moderate drinker	11 (13.3)	1 (4.8)	
Heavy drinker	17 (20.5)	1 (4.8)	
Very heavy drinker	13 (15.7)	0	
Body mass index (kg/m ²)	24 \pm 2	24 \pm 3	0.910
High sensitivity-C reactive protein (mg/dL)	0.63 \pm 2.5	0.17 \pm 0.32	0.516
Ejection fraction (%)	60 \pm 7	62 \pm 7	0.143
Total cholesterol (mg/dL)	171 \pm 33	156 \pm 36	0.076
HDL-cholesterol (mg/dL)	46 \pm 17	46 \pm 11	0.853
LDL-cholesterol (mg/dL)	107 \pm 30	98 \pm 35	0.240
Triglyceride (mg/dL)	170 \pm 99	120 \pm 84	0.038

HDL: high density lipoprotein, LDL: low density lipoprotein, Abstainer: fewer than 12 drinks in the past year, Light drinker: 2-3 drinks per month, Moderate drinker: 1-2 drinks per week, Heavy drinker: more than 3 drinks per week, Very heavy drinker: drinks almost every day¹³⁾

Fisher's exact test and Chi-square analysis were used for discrete data. Student's t-test was used for continuous variables. A $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Science (SPSS) version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

One hundred four patients, including 21 females, were included in this study. The baseline clinical characteristics of the patients are listed in Table 1. The female patients were younger than the male patients (52 ± 7 vs. 57 ± 10 years, $p = 0.046$). There were no significant differences between the male and female patients in the prevalence of hypertension, diabetes, and family history of coronary artery disease. However, the frequency of smoking and drinking was significantly higher in male patients than in female patients (65% vs. 19%, $p < 0.001$). Even after including passive and previous smoking histories, the prevalence of smoking was still higher in male patients (83% vs. 33%, $p < 0.001$). The frequency of alcohol consumption was also higher in the male patients than the female patients (89% vs. 43%, $p < 0.001$). The BMI was similar between the male and female patients (24 ± 2 vs. 24 ± 3 kg/m², $p = 0.910$). The ejection fractions measured by 2-dimensional echocardiogram, total cholesterol, low density lipoprotein (LDL)-cholesterol, and high density lipoprotein (HDL)-cholesterol levels were also similar. Although the mean triglyceride levels were within normal limits in both gender groups, the triglyceride levels were significantly higher in male patients (170 ± 99 vs. 120 ± 84 mg/dL, $p = 0.038$). The levels of hs-CRP, a known inflammatory marker, also did not differ between the gender groups. More than two-thirds of male patients and one-half of female patients had anginal attacks during rest, and there was no significant

difference in the prevalence of chest pain between the gender groups (78% vs. 57%, $p = 0.057$). Of the 104 patients, 7 patients (5 males and 2 females) visited the emergency room with non-ST elevation myocardial infarction and 3 male patients with ST-elevation myocardial infarction. Another male patient visited the emergency room after an aborted sudden death. Only 10 patients, including 3 females, had syncope with or without chest pain, and there were no significant differences between gender groups in its prevalence.

Provocation test

The angiographic characteristics are listed in Table 2. Significant organic stenosis of coronary arteries was observed in 4 of 21 female patients and 6 of the 83 male patients (19% vs. 7%, $p = 0.113$). Focal spasm was more common than diffuse spasm in both male and female patients (73% vs. 76%, $p = 0.802$). Multivessel spasm was rare in both genders (4% vs. 5%, $p = 1.00$). Right coronary artery was the most frequent site of coronary spasm in both genders and especially in male patients (90% vs. 67%, $p = 0.012$). The proximal portion of the coronary tree was a more frequent site of spasm than the distal portion in both genders. During spasm provocation tests, serious arrhythmias, such as complete atrioventricular block, ventricular tachycardia, and ventricular fibrillation were observed in 5 patients, and only 1 of whom was female.

Discussion

For many years in Korea, coronary spasm has been considered a disease of male cigarette smokers; however, female patients have frequently been diagnosed with coronary spasm in recent times. Therefore, we determined the clinical characteristics of female patients with coronary spasm. The results of this study showed that male

Table 2. Angiographic characteristics and provocation test data

	Male (n=83)	Female (n=21)	p
Organic stenosis $\geq 50\%$ in major coronary artery (%)	6 (7)	4 (19)	0.113
Focal spasm (%)	61 (73)	16 (76)	0.802
Proximal portion	38 (46)	10 (48)	0.819
Distal portion	26 (31)	6 (29)	
Diffuse spasm (%)	22 (27)	5 (24)	0.802
Single vessel spasm (%)	80 (96)	20 (95)	1.000
Multiple vessel spasm (%)	3 (4)	1 (5)	
Arrhythmia during spasm			0.598
3° atrioventricular block	1	0	
Ventricular tachycardia	1	1	
Ventricular fibrillation	2	0	
In the right coronary artery (%)	75 (90)	14 (67)	0.012
In the left circumflex artery (%)	5 (6)	1 (5)	0.651
In the left anterior descending artery (%)	7 (8)	7 (33)	0.007

smokers remained the majority of patients with coronary spasm, while only about one-fifth of patients were females. Previous studies of coronary spasm, including those from Korea and Japan, showed that smoking was the most important risk factor of coronary spasm, while other traditional risk factors for obstructive coronary artery disease, such as cholesterol and triglyceride levels were not.⁶⁻¹⁰ In this study, female patients also had lower rates of a positive smoking history and they were younger than male patients. The smoking rate in a general Korean female was also very low compared to that of a Korean male (4% vs. 52%).¹⁴ Furthermore, only four females in this study were active smokers and another three were passive smokers; they were housewives and their smoking husbands who smoked in their houses might be the main source of the passive smoke. The latter observation was consistent with a previous Japanese study.¹⁵ Moderate alcohol consumption has been associated with a lower risk of coronary heart disease.¹⁶ However, alcohol also is known to be occasionally associated with coronary spasm, although the mechanism is not clear.¹⁷ In this study, male patients consumed more alcohol than female patients. However, in the general population, the number of people who drink more than once per month was also much higher among male than female individuals (71% vs. 31%).¹⁴

Coronary spasm is usually known to be associated with atypical chest pain, especially in the early morning, and it is a frequent cause of acute coronary syndrome.¹¹ The proportions of the initial presentations as chest pain were not different between males and females. Serious clinical features of coronary spasm, such as acute myocardial infarction and syncope also did not differ between males and females. The incidence of serious arrhythmias observed during the induction of coronary spasm, such as atrioventricular block or ventricular tachyarrhythmias, were also similar between genders. These results may suggest that female patients with coronary spasm may have a similar prognosis as male patients with coronary spasm.

In our study, most of the patients had focal spasm. Different pathophysiologies have been suggested for focal and diffuse spasm. Localized endothelial dysfunction was related with focal spasm and coronary flow reserve was normal in patients with focal spasm; however, in patients with diffuse spasm, and coronary flow reserve was limited.¹⁸ Female patients had more diffuse spasms than focal spasms compared with male patients in a Japanese study,¹⁵ while in contrast to this Japanese study, female patients had more focal spasms than diffuse spasms in another Korean study.¹² In our study, there were no gender differences between the proportions of focal and diffuse spasm, and focal spasms were more common than diffuse spasms in both genders. Although the reason for these differences is not clear, use of different pro-

vocation test protocols might affect this result. In the Japanese study,¹⁵ they used initially acetylcholine and ergonovine was administered if coronary spasm had not been provoked by intracoronary injection of acetylcholine or the acetylcholine test was not initially selected. Ergonovine was used only in one-third of their patients. However, because acetylcholine is not available in Korea, only ergonovine was used in our study. It has been demonstrated that multiple spasms are provoked more readily with acetylcholine than ergonovine.¹⁹ Also, there are problems in determining whether spasm is focal or diffuse in the case of abrupt total occlusion of the proximal segment of a coronary artery without collateral flow. The difference of the study populations may be another explanation for the discrepancies in these results. For instance, female patients in this study were younger with a lower prevalence of diabetes than those in the Japanese study.¹⁴ Right coronary artery was the most frequent site of coronary spasm in our study, which stands in contrast with previous studies.^{20,21} In our study, the fact that ergonovine maleate was first injected into the right coronary arteries might have caused this discrepancy. Moreover, ergonovine was injected in both coronary arteries in patients with negative response as has been mentioned, while in the case of positive response after injection of ergonovine into the right coronary arteries, ergonovine was not injected into the left coronary arteries, although left coronary artery angiography was performed in those cases. We placed more emphasis on the gender differences in clinical characteristics rather than on differences in angiographic features themselves.

Study limitations

This study has some limitations that should be considered. First, the small sample size of female patients is the major limitation of this study, which may have been a source of selection bias. Second, we used a higher dosage of intracoronary ergonovine than the usual dosage used in other institutions.²² Third, some patients were lost during follow-up, and we could not determine differences in event rates, such as death and myocardial infarction between gender categories. Fourth, quantitative estimation of drinking was difficult.

Conclusion

Most patients with coronary spasm were smoking and drinking males. Female patients smoked and drank less and were younger than male patients. Other clinical characteristics were not different except for triglyceride levels. Further studies are needed to investigate the relevance of gender differences in the pathogenesis of the coronary spasm.

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REFERENCES

- 1) Hillis LD, Braunwald E. *Coronary-artery spasm*. *N Engl J Med* 1978;299:695-702.
- 2) Maseri A, L'Abbate A, Baroldi G, et al. *Coronary vasospasm as a possible cause of myocardial infarction: a conclusion derived from the study of "preinfarction" angina*. *N Engl J Med* 1978;299:1271-7.
- 3) Sueda S, Ochi N, Kawada H, et al. *Frequency of provoked coronary vasospasm in patients undergoing coronary arteriography with spasm provocation test of acetylcholine*. *Am J Cardiol* 1999;83:1186-90.
- 4) Shimokawa H, Nagasawa K, Irie T, et al. *Clinical characteristics and long-term prognosis of patients with variant angina: a comparative study between western and Japanese populations*. *Int J Cardiol* 1988;18:331-49.
- 5) Pristipino C, Beltrame JF, Finocchiaro ML, et al. *Major racial differences in coronary constrictor response between Japanese and Caucasians with recent myocardial infarction*. *Circulation* 2000;101:1102-8.
- 6) Caralis DG, Deligonul U, Kern MJ, Cohen JD. *Smoking is a risk factor for coronary spasm in young women*. *Circulation* 1992;85:905-9.
- 7) Sugiishi M, Takatsu F. *Cigarette smoking is a major risk factor for coronary spasm*. *Circulation* 1993;87:76-9.
- 8) Nobuyoshi M, Abe M, Nosaka H, et al. *Statistical analysis of clinical risk factors for coronary artery spasm: identification of the most important determinant*. *Am Heart J* 1992;124:32-8.
- 9) Takaoka K, Yoshimura M, Ogawa H, et al. *Comparison of the risk factors for coronary artery spasm with those for organic stenosis in a Japanese population: role of cigarette smoking*. *Int J Cardiol* 2000;72:121-6.
- 10) Cheon BW, Rha SW, Wani SP, et al. *Impact of smoking and smoking-related parameters on acetylcholine-induced coronary artery spasm*. *Korean Circ J* 2006;36:661-5.
- 11) Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M, Sechtem U. *Coronary artery spasm as a frequent cause of acute coronary syndrome*. *J Am Coll Cardiol* 2008;52:523-7.
- 12) Lee HC, Hong SR, Kim HS, et al. *The risk factors of vasospastic angina*. *Korean Circ J* 2002;32:224-32.
- 13) Austen WG, Edwards JE, Frye RL, et al. *A reporting system on patients evaluated for coronary artery disease: report of the Ad Hoc Committee for grading of coronary artery disease, council on cardiovascular surgery, American Heart Association*. *Circulation* 1975;51 (Suppl 4):5-40.
- 14) Korea National Statistics Office. *Report on the social statistics survey, 2006*. Available from: <http://www.nso.go.kr/>
- 15) Sueda S, Suzuki J, Watanabe K, et al. *Clinical characteristics of female patients with coronary spastic angina: comparison with male patients*. *Jpn Circ J* 2000;64:416-20.
- 16) Goldberg DM, Hahn SE, Parkes JG. *Beyond alcohol: beverage consumption and cardiovascular mortality*. *Clin Chem Acta* 1995;237:155-87.
- 17) Takizawa A, Yasue H, Omote S, et al. *Variant angina induced by alcohol ingestion*. *Am Heart J* 1984;107:25-7.
- 18) Akasaka T, Yoshida K, Hozumi T, et al. *Comparison of coronary flow reserve between focal and diffuse vasoconstriction induced by ergonovine in patients with vasospastic angina*. *Am J Cardiol* 1997;80:705-10.
- 19) Sueda S, Kohno H, Fukuda H, et al. *Clinical impact of selective spasm provocation tests: comparisons between acetylcholine and ergonovine in 1508 examinations*. *Coron Artery Dis* 2004;15:491-7.
- 20) Song JK, Park SW, Kang DH, et al. *Safety and clinical impact of ergonovine stress echocardiography for diagnosis of coronary vasospasm*. *J Am Coll Cardiol* 2000;35:1850-6.
- 21) Kim PJ, Seung KB, Kim DB, et al. *Clinical and angiographic characteristics of acute myocardial infarction caused by vasospastic angina without organic coronary heart disease*. *Circ J* 2007;71:1383-6.
- 22) Sueda S, Izoie Y, Kohno H, Fukuda H, Uraoka T. *Need for documentation of guidelines for coronary artery spasm: an investigation by questionnaire in Japan*. *Circ J* 2005;69:1333-7.