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Gender Differences in the Clinical Characteristics and Outcomes of Patients With Vasospastic Angina

– A Report From the Japanese Coronary Spasm Association –

Akiko Kawana, MD; Jun Takahashi, MD; Yusuke Takagi, MD; Satoshi Yasuda, MD; Yasuhiko Sakata, MD; Ryusuke Tsunoda, MD; Yasuhiro Ogata, MD; Atsushi Seki, MD; Tetsuya Sumiyoshi, MD; Motoyuki Matsui, MD; Toshikazu Goto, MD; Yasuhiko Tanabe, MD; Shozo Sueda, MD; Norifumi Kubo, MD; Shin-ichi Momomura, MD; Hisao Ogawa, MD; Hiroaki Shimokawa, MD on Behalf of the Japanese Coronary Spasm Association

Background: Accumulating evidence has demonstrated the gender differences in the clinical characteristics and outcomes of patients with ischemic heart disease. However, it remains to be elucidated whether it is also the case for vasospastic angina (VSA).

Methods and Results: We enrolled a total of 1,429 VSA patients (male/female, 1090/339; median age 66 years) in our nationwide multicenter registry by the Japanese Coronary Spasm Association. As compared with male patients, female patients were characterized by older age (median 69 vs. 66 years), lower incidence of smoking (20% vs. 72%) and less significant organic stenosis (9% vs. 16%) (all P=0.001). Multivariate analysis demonstrated that the predictors of major adverse cardiac events (MACE) were considerably different by genders; women were more associated with age and electrical abnormalities, whereas men with structural abnormalities. Overall 5-year MACE-free survival was comparable between both genders. However, when the patients were divided into 3 groups by age [young (<50 years), middle-aged (50–64 years) and elderly (≥65 years)], the survival was significantly lower in the young female group (young 82%, middle-aged 92%, elderly 96%, P<0.01), where a significant interaction was noted between age and smoking. In contrast, the survival was comparable among the 3 age groups of male patients.

Conclusions: These results indicate that there are gender differences in the characteristics and outcomes of VSA patients, suggesting the importance of gender-specific management of the disorder. (*Circ J* 2013; **77:** 1267–1274)

Key Words: Gender difference; Prognosis; Vasospastic angina

During the past several decades, gender differences in patients with ischemic heart disease (IHD) have been repeatedly demonstrated, in terms of the prevalence, symptom manifestation, pathophysiology and long-term prognosis.[1–4] Indeed, female IHD patients, as compared with male IHD patients, have a lower prevalence of organic coronary lesions but a higher prevalence of symptoms, ischemia, and adverse outcomes.[5–7] Furthermore, accumulating evidence has indicated that the paradoxical gender difference is linked to functional abnormalities of the coronary artery. WISE (Women's Ischemic Syndrome Evaluation) and related studies demonstrated that abnormal coronary reactivity and microvascular dysfunction are substantially involved not only in the development of IHD but also the prognosis, of IHD in women.[8,9] Furthermore, women commonly develop a variety of generalized vascular disorders, such as migraine, Raynaud's phenom-

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Tohoku University Graduate School of Medicine, Sendai (A.K., J.T., Y. Takagi, Y.S., H.S.); National Cerebral and Cardiovascular Center, Suita (S.Y.); Japanese Red Cross Kumamoto Hospital (R.T., Y.O.), Kumamoto; Sakakibara Heart Institute, Tokyo (A.S., T.S.); Yamagata Prefectural Central Hospital, Yamagata (M.M., T.G.); Niigata Prefectural Shibata Hospital, Shibata (Y. Tanabe); Ehime Prefectural Niihama Hospital, Niihama (S.S.); Jichi Medical University Saitama Medical Center, Saitama (N.K., S.M.); and Kumamoto University Graduate School of Medical Sciences, Kumamoto (H.O.), Japan

Other investigators collaborating in this study and their institutions are listed in the Appendix (**Data S1**).

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Mailing address: Hiroaki Shimokawa, MD, Professor and Chairman, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan. E-mail: shimo@cardio.med.tohoku.ac.jp

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Table 1. Demographic Characteristics of VSA Patients by Gender

	Male	Female	P value
n (%)	1,090 (76)	339 (24)	<0.001
Age, median (IQR), years	66 (58, 72)	69 (60, 75)	<0.001
Coronary risk factors, n (%)			
Hypertension	511 (47)	155 (46)	0.38
Dyslipidemia	481 (44)	166 (49)	0.07
Diabetes mellitus	186 (17)	47 (14)	0.09
Smoking	781 (72)	67 (20)	<0.001
No. of risk factors, mean (SD)	1.80 (1.02)	1.28 (0.96)	<0.001
Family history of IHD, n (%)	118 (11)	50 (15)	0.03
Previous MI, n (%)	81 (7)	10 (3)	0.003
Spontaneous angina attack			
ST-segment change, n (%)			
ST elevation	234 (21)	38 (11)	<0.001
ST depression	83 (8)	38 (11)	0.03
Arrhythmic event, n (%)			
PVC	12 (1)	2 (1)	0.32
VT/VF	14 (2)	3 (1)	0.40
AV block	19 (2)	2 (1)	0.09
Bradycardia/sinus pause	20 (2)	8 (2)	0.34
OHCA*	30 (3)	5 (1)	0.13

*Complicated by VT/VF (M/F: 23/3).
AV, atrioventricular; IHD, ischemic heart disease; IQR, interquartile range; MI, myocardial infarction; OHCA, out-of-hospital cardiac arrest; PVC, premature ventricular contraction; VF, ventricular fibrillation; VSA, vasospastic angina; VT, ventricular tachycardia.

enon and autoimmune arteritis.[10] These previous findings suggest that female hormone levels, which vary in conjunction with ovarian cycle, pregnancy, peripartum and menopause, may have close relationship with vascular function in both healthy and diseased women.[11]

Coronary vasospasm, which is caused by abnormal coronary hyperreactivity, plays an important role in the pathogenesis of a wide variety of IHD.[12,13] Although it has been considered that there are substantial racial differences in the prevalence of vasospastic angina (VSA), with a higher incidence in the Japanese population,[14] a recent study suggested a higher prevalence of VSA even in Caucasian patients than ever considered.[15] It has been also demonstrated that the prevalence of VSA is higher in men than in women.[16–18] However, it remains to be elucidated whether there are gender differences in the clinical characteristics and long-term prognosis of VSA. Thus, in the present study, we addressed this important issue in the nationwide multicenter study conducted by the Japanese Coronary Spasm Association.

Methods

The Japanese Coronary Spasm Association was founded in 2006 and currently consists of 81 institutes.[19,20] The present study was approved by the institutional review boards or ethics committees of all participating institutes.

Study Subjects

All VSA patients were diagnosed between April 1, 2003 and December 31, 2008 at the participating institutes and were registered in the database of the Japanese Coronary Spasm Association.[19,20] The registration period was from September 1, 2007 to December 31, 2008. Thus, data collection of this study was conducted in a retrospective fashion for patients diagnosed before September 2007 and in a prospective manner for those diagnosed after that date.[19,20] During the registration period, a total of 1,528 patients were registered from 47 institutes. However, 99 patients were excluded because they did not fulfill the diagnosis criteria as required by the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina of the Japanese Circulation Society (JCS).[21] Finally, 1,429 VSA patients (male, n=1,090 and female, n=339) were analyzed in the present study.

Diagnosis of VSA

Based on the Guidelines of the Japanese Circulation Society,[21] the diagnosis of VSA was made by spontaneous attack only without provocation test (n=185) or spasm provocation tests (provocation tests alone, n=1,122 and both provocation tests and spontaneous attack, n=122). According to the JCS Guidelines, the definition of spontaneous attack was a chest pain at rest and/or on effort, accompanied by transient ST-segment elevation or depression of more than 0.1 mV or a newly appearance of negative U wave on ECG.[21] Positive provocation test was defined as a total or subtotal (≥90%) coronary artery narrowing induced by pharmacological (eg, acetylcholine and/or ergonovine) or non-pharmacological (eg, hyperventilation) challenge during coronary angiography, accompanied by chest pain and/or ischemic ECG changes. The type of coronary spasm during the provocation test was classified into focal, diffuse and mixed type, as previously described.[20]

Data Collection

The demographic and clinical data were collected in the central database system through the internet.[19,20] The investigated items included age, sex, coronary risk factors, types of angina episodes, ST-segment changes and arrhythmias during spontaneous attacks, angiographic findings and arrhythmic compli-

Table 2. Results of Coronary Spasm Provocation Tests

	Male (n=938)	Female (n=306)	P value
Provocation test, n (%)			
Acetylcholine	489 (52)	224 (73)	<0.001
Ergonovine	423 (45)	74 (24)	<0.001
Acetylcholine+ergonovine	17 (1.8)	6 (1.9)	0.99
Others	9 (0.9)	2 (0.6)	0.74
Organic stenosis >50%, n (%)	170 (16)	31 (9)	0.001
Spasm-positive artery, n (%)			
LAD	468 (50)	198 (65)	<0.001
Diffuse/focal	262 (59)/180 (41)	113 (61)/73 (39)	0.40
LCX	253 (27)	64 (21)	0.02
Diffuse/focal	155 (66)/80 (34)	45 (78)/13 (22)	0.06
RCA	535 (57)	158 (52)	0.06
Diffuse/focal	277 (56)/221 (44)	82 (59)/57 (41)	0.27
Multivessel	279 (30)	95 (31)	0.36
Diffuse/focal/mixed	151 (56)/57 (21)/60 (22)	63 (69)/14 (15)/14 (15)	0.10
Arrhythmic complication, n (%)			
PVC	10 (1)	3 (1)	0.60
VT/VF	24 (3)	16 (5)	0.02
AV block	6 (1)	2 (1)	0.62
Bradycardia/sinus pause	17 (2)	11 (4)	0.06

Results obtained from 1,244 patients (M/F: 938/306) who underwent spasm provocation testing.
LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery. Other abbreviations as in Table 1.

cations of the spasm provocation tests, medications and device therapy such as implantable cardioverter defibrillator (ICD). Hypertension, dyslipidemia and diabetes mellitus were diagnosed based on the Guidelines of the Japanese Society of Hypertension, Japan Atherosclerosis Society, and Japan Diabetes Society, respectively. The clinical outcomes during the follow-up period were also collected. Ventricular tachycardia (VT) was defined as 3 or more consecutive premature ventricular contractions (PVCs). In this database, sustained and non-sustained VT were not differentiated and VT and ventricular fibrillation (VF) were classified in the same category. Atrioventricular (AV) block consisted of second- and third-degree AV block and bradycardia was defined as sinus rhythm <50 beats/min. Out-of-hospital cardiac arrest (OHCA) was defined as cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[19,20]

Endpoints

The primary endpoint was major adverse cardiac events (MACE), including cardiac death, nonfatal myocardial infarction (MI), hospitalization due to unstable angina pectoris and heart failure and appropriate ICD shocks during the follow-up period. The secondary endpoint was all-cause mortality. The definitions of these events was previously described.[20]

Statistical Analysis

Continuous variables are presented as median and interquartile range (IQR), and categorical variables are described as percentages. Group comparisons were performed with the Mann-Whitney test for continuous variables, Chi-square test or Fisher's exact test for categorical variables, and log-rank test for survival curves. The Kaplan-Meier method was used to analyze survival rate free from death and MACE. Multivariable Cox proportional hazard model was applied to determine the correlated factors with MACE by sex. The proportional hazards assumption was examined with the log minus log plot. Hazard ratio and 95% confidence interval (CI) were calculated. A P value <0.05 or P for interaction <0.2 was considered to be statistically significant. The statistical analysis was performed with SPSS 18.0 (SPSS Inc, Chicago, IL, USA).

Results

Gender Differences in Demographic Characteristics

Male and female patients accounted for about three-fourths and one-fourth of all the VSA patients, respectively (male n=1,090, female n=339). The demographic characteristics by gender are summarized in Table 1. Female patients were older than male patients (median 69 vs. 66 years, P<0.001). Although there was no gender difference in the prevalence of hypertension, dyslipidemia and diabetes mellitus, the prevalence of smoking history (20% vs. 72%, P<0.001) and a total number of risk factors (1.28±0.96 vs. 1.80±1.02, P<0.001) were significantly lower among the female patients. Moreover, as compared with the male patients, the female patients had a lower incidence of previous myocardial infarction and a higher incidence of a family history of IHD. Among the 1,429 patients, ECG was successfully recorded in 1,317 patients during spontaneous angina attacks, and 393 of them showed significant ST-segment changes. ST-segment depression was documented more frequently in female patients, while ST-segment elevation more commonly in male patients. There was no significant gender difference in the occurrence of arrhythmic events during spontaneous angina attacks, including VT/VF and OHCA.

Angiographic Findings and Arrhythmias During Spasm Provocation Tests

Spasm provocation tests were performed in 938 male patients and 306 female patients during coronary angiography, with a

Table 3. Medical Treatment of VSA Patients by Gender

	Male (n=1,090)	Female (n=339)	P value
Medication			
Calcium-channel blocker, n (%)	1,020 (94)	311 (92)	0.15
Nitrate, n (%)	518 (48)	177 (52)	0.07
Antiplatelet, n (%)	540 (50)	129 (38)	<0.001
Statin, n (%)	347 (32)	125 (37)	0.049
ACEI/ARB, n (%)	271 (25)	69 (20)	0.05
β-blocker, n (%)	48 (4)	13 (4)	0.39
Dose reduction/discontinuation	7 (2)	18 (1.6)	0.63

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. Other abbreviation as in Table 1.

Table 4. Clinical Outcome of VSA Patients by Gender

	Male (n=1,090)	Female (n=339)	P value
MACE, n (%)	66 (6)	19 (6)	0.44
Cardiac death	5 (0.5)	1 (0.3)	0.56
Nonfatal MI	7 (1)	2 (1)	0.64
Unstable angina	53 (5)	15 (4)	0.44
Heart failure	3 (0.3)	1 (0.3)	0.66
Appropriate ICD shock	1 (0.1)	1 (0.3)	0.42
All-cause death, n (%)	17 (2)	2 (1)	0.14

ICD, implantable cardioverter defibrillator; MACE, major adverse cardiac event. Other abbreviations as in Table 1.

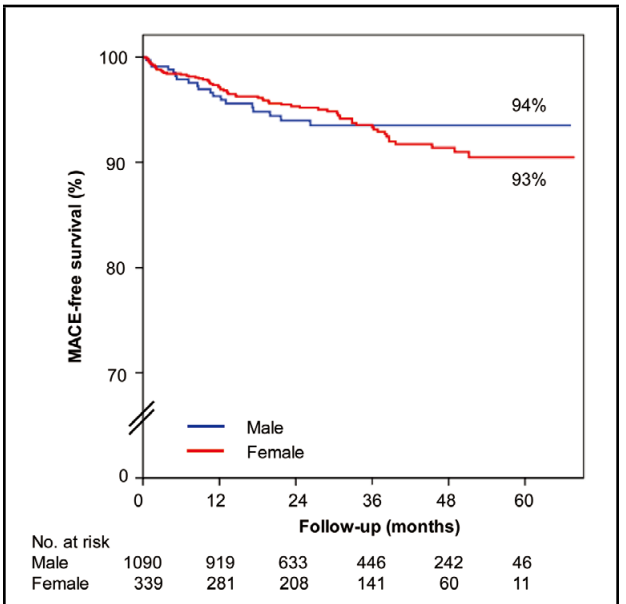

Figure 1. Kaplan-Meier curves by gender for MACE in VSA patients. The MACE-free survival rate was comparable between female (red line, n=339) and male (blue line, n=1,090) VSA patients. MACE included cardiac death, nonfatal myocardial infarction, hospitalization for heart failure and unstable angina pectoris, and appropriate ICD shocks. MACE, major adverse cardiac events; ICD, implantable cardioverter defibrillator; VSA, vasospastic angina.

comparable performance rate between genders (male 85% vs. female 90%, n.s.). The results of spasm provocation tests are summarized in Table 2. The spasm provocation test was performed others acetylcholine (male 52% vs. female 73%, P<0.001), ergonovine (male 45% vs. female 24%, P<0.001), both of them (male 1.8% vs. female 1.9%, n.s.), or others (eg, hyperventilation, male 0.9% vs. female 0.6%, n.s.). Significant organic stenosis, defined as more than 50% luminal narrowing by coronary angiography, was less common in female patients than in male patients (9% vs. 16%, P<0.001). During spasm provocation test, coronary spasm was more frequently induced in the left anterior descending coronary artery (LAD) in female patients, whereas the left circumflex coronary artery (LCX) more commonly in male patients. The prevalence of multivessel spasm and the form of coronary vasoconstriction (eg, diffuse or focal type) were comparable between both genders. In contrast, as compared with male patients, female patients more frequently associated with VT or VF during the spasm provocation test (5% vs. 3%, P=0.02).

Medical Treatment

The comparison of medications by gender is shown in Table 3. The prescription rate of calcium-channel blockers (CCBs), the first-line agent for the treatment of VSA, was high and comparable between male and female patients (94% vs. 92%). Reflecting the baseline characteristics, statins were more frequently prescribed in female than in male patients (37% vs. 32%, P=0.049), and the use of antiplatelet agents was less frequent in female patients (38% vs. 50%, P<0.001). There were no significant differences in the use of long-acting nitrate, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or β-blockers between the genders. Additionally, the rate of the patients in whom medications were reduced or discontinued during the follow-up period was low and comparable in both genders (Table 3).

Clinical Outcomes and Prognostic Factors of MACE

During the median follow-up period of 32 months (IQR: 17–46 months), 66 male patients (6.1%) and 19 female patients (5.6%) reached the primary endpoint of MACE, and all-cause death as the secondary endpoints occurred in only 17 male patients (1.6%) and 2 female (0.6%) (Table 4). The 5-year survival rate free from MACE was also comparable between both genders (male 94% vs. female 93%, n.s.) (Figure 1). However, the multivariate Cox proportional hazard model, in which each variable was individually adjusted for age and organic stenosis, demonstrated that the correlated factors with MACE were considerably different between the genders (Table 5). Male patients were was more associated with structural abnormali-

Table 5. Prognostic Factors of MACE by Multivariate Analysis

	Male			Female		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.01	0.98–1.03	0.59	0.94	0.91–0.98	0.002
Hypertension	0.69	0.42–1.14	0.14	2.13	0.84–5.42	0.11
Dyslipidemia	0.94	0.57–1.54	0.80	2.18	0.85–5.61	0.11
Diabetes mellitus	1.43	0.80–2.56	0.23	1.74	0.57–5.31	0.33
Smoking	2.13	1.08–4.17	0.03	1.67	0.62–4.53	0.31
Previous MI	2.22	1.08–4.55	0.03	0	0.00–0.00	0.98
ST elevation	1.63	0.96–2.75	0.07	1.57	0.51–4.82	0.43
ST depression	1.33	0.61–2.94	0.47	0	0.00–0.00	0.97
Organic stenosis	2.38	1.38–4.10	0.002	1.62	0.46–5.64	0.45
VT/VF (non-OHCA)	0	0.00–0.00	0.97	8.66	1.13–66.5	0.04
History of OHCA	4.36	1.72–11.0	0.002	1.73	0.20–15.3	0.62
LAD spasm	1.19	0.68–2.07	0.54	1.29	0.46–3.64	0.64
LCX spasm	0.92	0.49–1.74	0.80	1.44	0.51–4.08	0.50
RCA spasm	1.10	0.63–1.93	0.74	1.74	0.67–4.50	0.26
Multivessel spasm	1.41	0.79–2.50	0.24	2.46	0.96–6.28	0.06
Antiplatelet	1.37	0.82–2.29	0.22	0.87	0.32–2.31	0.78
Statin	1.36	0.81–2.27	0.23	0.32	0.09–1.11	0.074
β-blocker	1.57	0.62–4.00	0.34	3.20	0.71–14.4	0.13

Each variable was individually adjusted for age and organic coronary stenosis in the Cox model.
CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,2,4.

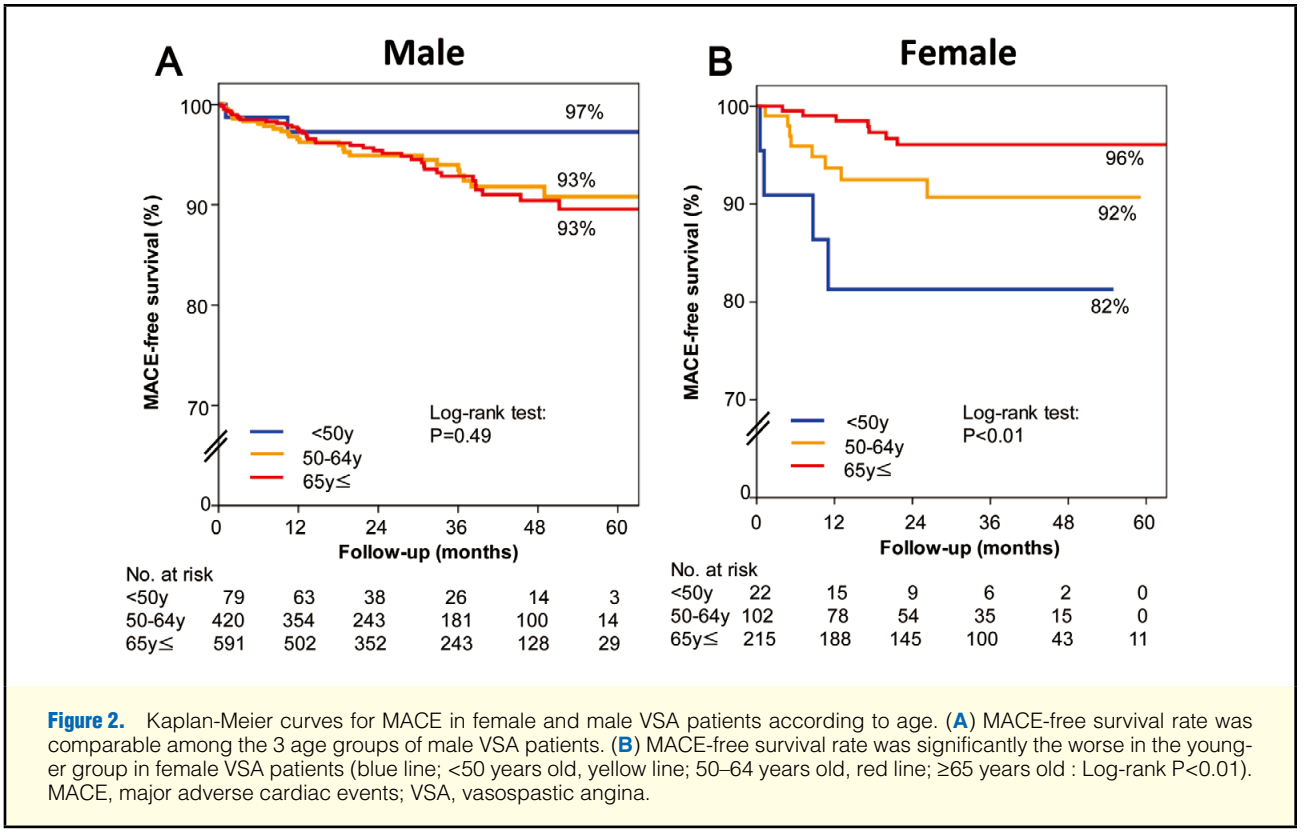

Figure 2. Kaplan-Meier curves for MACE in female and male VSA patients according to age. (**A**) MACE-free survival rate was comparable among the 3 age groups of male VSA patients. (**B**) MACE-free survival rate was significantly the worse in the younger group in female VSA patients (blue line; <50 years old, yellow line; 50–64 years old, red line; ≥65 years old : Log-rank P<0.01). MACE, major adverse cardiac events; VSA, vasospastic angina.

ties such as organic coronary stenosis and previous myocardial infarction, in addition to other established prognostic factors (eg, smoking and history of OHCA), whereas female patients with age and electrical abnormalities such as VT/VF during spontaneous angina attack. Importantly, we found a significant negative influence of age on the prognosis of female VSA patients.

Different Prognoses of Female Patients by Age

To examine the differences in the prognosis of VSA patients

Table 6. Gender Difference in the Clinical Characteristics of VSA Patients by Age

	Male				Female			
	<50 (n=79)	50–64 (n=420)	65≤ (n=591)	P value	<50 (n=22)	50–64 (n=102)	65≤ (n=215)	P value
Risk factor n (%)								
Hypertension	39 (38)	206 (49)	275 (46)	0.19	6 (27)	40 (39)	109 (50)	0.03
Dyslipidemia	36 (45)	199 (47)	246 (41)	0.19	5 (22)	53 (51)	108 (50)	0.04
Diabetes mellitus	9 (11)	67 (16)	110 (18)	0.21	1 (4)	15 (14)	31 (14)	0.42
Smoking	54 (68)	318 (75)	409 (69)	0.06	12 (54)	25 (24)	31 (13)	<0.001
Previous MI	8 (10)	31 (7)	42 (7)	0.63	1 (4)	3 (2)	6 (2)	0.65
Family history of IHD	12 (15)	54 (12)	52 (8)	0.05	7 (31)	7 (31)	28 (13)	0.06
Family history of sudden death	1 (1)	3 (0.7)	7 (1)	0.74	0 (0)	0 (0)	5 (2)	0.84
Medical treatment, n (%)								
Calcium-channel blocker	75 (94)	405 (96)	540 (91)	0.006	20 (90)	97 (95)	194 (90)	0.37
Nitrate	48 (60)	160 (38)	310 (52)	<0.001	11 (50)	53 (51)	113 (52)	0.98
Antiplatelet	41 (51)	200 (47)	299 (50)	0.58	6 (27)	35 (34)	88 (40)	0.29
Statin	24 (30)	135 (32)	188 (31)	0.95	4 (18)	37 (36)	84 (39)	0.15
ACEI/ARB	22 (27)	90 (21)	159 (26)	0.11	2 (9)	15 (14)	52 (24)	0.06
β-blocker	0 (0)	12 (2.8)	36 (6)	0.008	1 (4)	2 (1.9)	10 (4.6)	0.56

Abbreviations as in Tables 1,3.

by age and gender, we divided them into 3 age groups (young group, <50 years, intermediate group, 50–64 years, and elderly group, ≥65 years). Kaplan-Meier curves for MACE stratified by the 3 groups by age are shown in **Figure 2**. Although there was no significant difference in the MACE-free survival among the 3 age groups of male patients, it was significantly lower in the young group as compared with the other 2 groups in female patients (**Figure 2**). The gender differences in clinical characteristics and medical treatment of VSA patients by age are summarized in **Table 6**. The prescription rates of medications with a favorable prognosis for IHD patients, including CCBs, antiplatelet agents, statins and β-blockers, were comparable among the 3 age groups of female patients. Importantly, in female patients, the prevalence of smoking was highest in the young group compared with the other 2 groups, whereas the prevalence of hypertension and hyperlipidemia was higher in the latter 2 groups. Indeed, in female patients, there was a significant interaction between age (≥60 years) and smoking for the occurrence of MACE, whereas no such interaction was noted for male patients.

Discussion

The major findings of the present study were as follows. (1) There were substantial gender differences in the clinical characteristics of VSA patients, including age and the prevalence of smoking and significant organic stenosis. (2) Although there was no significant gender difference in 5-year MACE-free survival, the prognostic factors of MACE were considerably different between the genders. (3) In the female patients, the long-term prognosis was lowest in young female group with a significant interaction noted with smoking. These results indicate that there are substantial gender differences in VSA patients, suggesting the importance of gender-specific management of the disorder.

Gender Differences in the Clinical Characteristics of VSA Patients

Previous studies demonstrated a higher prevalence of male gender in VSA patients[16–18] and only a few studies examined the possible gender difference of the disorder.[22,23] In Japan, the general population has rapidly westernized and aging,[3,24] which could change the clinical characteristics of VSA patients, especially those of female VSA patients. In the present study, the female VSA patients had lower prevalences of smoking, old myocardial infarction and organic coronary artery disease as compared with male patients, a consistent findings with the previous study.[22] Since women are generally protected from atherosclerosis by female hormones,[1,25,26] it is expected that female VSA patients had lower prevalence of organic coronary stenosis compared with male patients despite the higher age. The extent of atherosclerotic change of the coronary artery could influence the development of coronary spasm as there is a close topological relationship between coronary vasospasm and atherosclerosis in both animal models[27] and humans.[28–30] In the present study, we found no gender difference in the proportions of focal and diffuse spasm during provocation test, while it was previously reported that diffuse spasm was more common in female patients.[22] Because focal spasm could occur more frequently at the relatively advanced atherosclerosis lesions[31] and our female VSA patients were older than those in the previous study by 5 years,[22] the present finding of no gender difference in spasm type could be explained, at least in part, by the advanced coronary atherosclerosis in female patients.

Gender Differences in Prognostic Factors of MACE

Although it was previously reported that insufficient medical therapy was responsible for poor prognosis of female patients with acute coronary syndrome,[32] the female VSA patients were adequately treated with good compliance and without gender difference in the present study. Especially, CCBs, which are recommended at the first-line therapy by the JCS Guidelines,[21] were prescribed to more than 90% of patients in both genders. Under these guideline-based medical therapies,[33–35] no gender difference was noted for the 5-years MACE-free survival and all-cause death. However, the prognostic factors of MACE were markedly different between the genders; the prognosis of female patients was more associated with age and electrical abnormalities (eg, VT/VF during spontaneous attack),

whereas that of male patients with structural abnormalities (eg, organic stenosis, previous MI). While our present findings with male VSA patients are consistent with the previous studies,[16–19] those with female VSA patients are novel findings. Life-threatening ventricular arrhythmias during VSA attacks could cause sudden cardiac death.[36] Indeed, we have recently demonstrated that the VSA patients who survive OHCA are a particularly high-risk population.[19,37] However, in the present study, OHCA was a significant prognostic factor for male patients but not in female patients. Although the precise mechanisms remain to be examined, it is conceivable that a gender difference in myocardial electrical properties may be involved.[38,39]

Gender Difference in the Clinical Characteristics and Outcomes of VSA Patients by Age

One of the novel findings of the present study is that young age (<50 years) was a significant negative prognostic factor in female patients but not in male patients. As discussed above, women are generally protected from atherosclerosis by female hormones before menopause with less prevalence of cardiovascular disease as compared with men.[1,25,26] Furthermore, it has been reported that in premenopausal female VSA patients, angina attacks correlate with the menstrual cycle with a cyclic variation in endothelial function.[40,41] The present study provides important evidence that smoking habit shows a significant interaction with age as the prevalence of smoking was highest in the young female group. Although it was previously demonstrated that smoking is an important risk factor for coronary spasm in premenopausal women,[42] the present study demonstrates for the first time the significant interaction between smoking and age for female VSA patients in a large number of patients. We have previously demonstrated that Rho-kinase, which has been identified as one of the effectors of the small GTP-binding protein Rho, plays a key role in the molecular mechanisms of VSA.[43] Indeed, we were able to demonstrate that nicotine potently upregulates Rho-kinase in human coronary artery smooth muscle cells, while estrogens potently downregulate it.[44] We also have recently demonstrated that Rho-kinase activity in circulating neutrophils is a useful biomarker for diagnosis and disease activity assessment of VSA.[45] Thus, this measurement may help to tailor-made management of VSA patients.

Study Limitations

Several limitations should be mentioned for the present study. First, the study is based on the retrospective and prospective data. Moreover, as retrospective population dominated, it was difficult to prove a causal relationship. We are now conducting a prospective multicenter registry study of VSA patients, which will enable us to further evaluate gender differences in VSA in the future. Second, the present study emplayed an unusual composite primary endpoint that included appropriate ICD shocks, due to specific nature of VSA. Third, the present study only examined the data for patients with epicardial coronary spasm, but not those with microvascular angina.[46] The gender difference in microvascular angina remains to be examined in future studies. Fourth, in the present study, no information was available on menopause in female patients. Fifth, gender differences in the agent or precedure of spasm provocation test could affect some results of the present study. The additional information on menopause in the on-going prospective study will further elucidate the effects of menopause on the gender differences in VSA patients.

Conclusions

In the present multicenter study by the Japanese Coronary Spasm Association, we were able to demonstrate that there are substantial gender differences in VSA patients, suggesting the importance of gender-specific management of the disorder.

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Disclosures

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Supplementary Files

Supplementary File 1

Data S1. Appendix

Please find supplementary file(s);
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