Clinical Characteristics and Long-Term Prognosis of Vasospastic Angina Patients Who Survived Out-of-Hospital Cardiac Arrest

Multicenter Registry Study of the Japanese Coronary Spasm Association

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Background—Coronary artery spasm plays an important role in the pathogenesis of ischemic heart disease; however, its role in sudden cardiac death remains to be fully elucidated. We examined the clinical characteristics and outcomes of patients with vasospastic angina (VSA) in our nationwide multicenter registry by the Japanese Coronary Spasm Association.

Methods and Results—Between September 2007 and December 2008, 1429 patients with VSA (male/female, 1090/339; median, 66 years) were identified. They were characterized by a high prevalence of smoking and included 35 patients who survived out-of-hospital cardiac arrest (OHCA). The OHCA survivors, as compared with the remaining 1394 non-OHCA patients, were characterized by younger age (median, 58 versus 66 years; $P<0.001$) and higher incidence of left anterior descending coronary artery spasm (72% versus 53%, $P<0.05$). In the OHCA survivors, 14 patients underwent implantable cardioverter-defibrillator (ICD) implantation while intensively treated with calcium channel blockers. Survival rate free from major adverse cardiac events was significantly lower in the OHCA survivors compared with the non-OHCA patients (72% versus 92% at 5 years, $P<0.001$), including appropriate ICD shocks for ventricular fibrillation in 2 patients. Multivariable analysis revealed that OHCA events were significantly correlated with major adverse cardiac events (hazard ratio, 3.25; 95% confidence interval, 1.39 to 7.61; $P<0.01$).

Conclusions—These results from the largest vasospastic angina cohort indicate that vasospasm patients who survived OHCA are high-risk population. Further studies are needed to determine whether implantable cardioverter-defibrillator therapy improves patient prognosis. (*Circ Arrhythm Electrophysiol*. 2011;4:295-302.)

Key Words: acetylcholine ■ angina pectoris ■ arrhythmia, cardiac ■ prognosis ■ coronary vasospasm

Out-of-hospital cardiac arrest (OHCA) is a major public health problem. Its estimated number is 300 000 to 400 000 per year in the United States.[1] A prospective study showed an incidence of 53 in 100 000 per year, with 25% of victims being younger than 65 years.[2] Causes of OHCA are strongly associated with coronary artery disease as evidenced at autopsy, and the survival rate from OHCA still remains to be substantially improved.[1] Importantly, a significant number of OHCA cases remained unexplained if victims have no structural abnormalities (eg, organic coronary stenosis) in the postmortem analysis.[3] This finding strongly suggests that

functional abnormalities of the coronary artery are also involved in the pathogenesis of OHCA.[4]

Clinical Perspective on p 302

Recently, the prevalence of early access to emergency medical service, early bystander cardiopulmonary resuscitation, and early defibrillation has been increasing, with a resultant improvement of the survival rate from OHCA.[5–7] The progress of the chain of survival now opens the window to elucidate the underlying mechanisms of patients who survived OHCA. Coronary artery spasm plays an important

role in the pathogenesis of a wide variety of ischemic heart disease, including sudden cardiac death, and thus could be one of the most important functional abnormalities of the coronary artery.[8–10] However, little is known about the clinical characteristics including sex difference and long-term prognosis of patients with vasospastic angina (VSA) who survived OHCA, except for the previous single-center studies with a small number of patients.[11,12]

In the present study, we thus conducted the nationwide multicenter registry study with the large patient number by the Japanese Coronary Spasm Association to elucidate the clinical characteristics and long-term prognosis of VSA patients, especially those who survived OHCA.

Methods

The Japanese Coronary Spasm Association was founded in 2006, and currently 68 institutes participate. The present study was approved by the institutional review boards or ethics committees of all participating institutions.

Study Patients

All VSA patients were referred or admitted to the participating institutes and were originally diagnosed between April 1, 2003, and December 31, 2008. The registration was made between September 1, 2007, and December 31, 2008. In the present study, data collection was conducted in a retrospective fashion for patients seen before September 2007 and in a prospective manner for those seen after that date. The diagnosis of VSA was made based on the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina of the Japanese Circulation Society.[13] The definition of VSA included an angina attack at rest and/or on effort, accompanied by a transient ECG ST-segment elevation or depression of >0.1 mV or a newly appearance of negative U wave in at least 2 related leads, and/or a total or subtotal coronary artery narrowing during the provocation test of coronary spasm, accompanied by chest pain and/or ischemic ECG changes mentioned above.

Data Collection

The demographic and clinical data were submitted to a central data base, including age, sex, coronary risk factors, family history, type of angina episodes, circadian distribution of angina attacks, leads of ST-segment elevation or depression and arrhythmias during spontaneous or provoked angina attack, location of coronary spasm, device therapy such as implantable cardioverter-defibrillator (ICD), medical therapy, and its adherence. We defined reduction and discontinuation of medication as having a gap in use of any medication and no use of medication, respectively. Hypertension, dyslipidemia, and diabetes mellitus were diagnosed on the basis of guidelines of the Japanese Society of Hypertension, Japan Atherosclerosis Society and the Japan Diabetes Society, respectively.[14–16] Significant coronary stenosis was defined as >50% of luminal narrowing of major coronary arteries evaluated by coronary angiography. OHCA was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[17]

End Points

The primary end point was major adverse cardiac events (MACE), including cardiac death, nonfatal myocardial infarction, hospitalization for unstable angina pectoris and heart failure, and appropriate ICD shocks during the follow-up period, which began at the date of original VSA diagnosis. The secondary end point was all-cause mortality. Cardiac death was defined as sudden death (ie, death occurring unexpectedly without any apparent symptoms or within 1 hour of symptom onset or nonwitnessed death in the absence of any other possible cause) or death associated with acute myocardial infarction. Acute myocardial infarction was defined in patients with prolonged (>30 minutes) chest pain, associated with ST-segment changes and elevated levels of cardiac enzymes. Unstable angina pectoris was diagnosed if chest discomfort or pain became recurrent or worsening along with ischemic ECG changes. Heart failure was diagnosed if a patient showed signs of exertional dyspnea, orthopnea, rales in more than one-third of the lung fields, elevated jugular venous pressure, or pulmonary congestion on chest radiography related to cardiac dysfunction.

Statistics

Continuous variables are presented as medians and interquartile ranges and categorical variables as percentages. Group comparisons were performed with Mann-Whitney test for continuous variables, Fisher exact test for categorical variables, and log-rank test for survival curves. Survival free from death and MACE was analyzed by the Kaplan–Meier method. Multivariable analysis of correlated factors of MACE was performed with a Cox proportional hazard model. Variables depicted by univariable analysis to be correlated with MACE and well-known predictive variables were subjected to the forced entry method. The proportional hazards assumption was examined with the log minus log plot. Hazard ratio and 95% confidence intervals were also calculated. A value of $P<0.05$ was considered to be statistically significant.

Results

Clinical Characteristics of Patients With VSA

Among a total of 1528 VSA patients registered from 47 institutes, 99 patients were excluded because they did not meet the diagnostic criteria (n=7) or the inclusion criteria (n=92). Finally, 1429 patients were studied (online-only Data Supplement Figure 1). The clinical characteristics of those patients are summarized in Table 1. Among the coronary risk factors, smoking was observed most frequently (≈60%), especially in male patients. The prevalence of family history of ischemic heart diseases, previous myocardial infarction, and the existence of organic coronary stenosis was relatively low (≈10%). When compared with the female patients, the male patients were characterized by younger age, higher incidences of previous myocardial infarction, organic coronary stenosis, angina attack with ST-segment elevation, and lower incidence of family history of ischemic heart diseases. In contrast, no sex difference was noted in the prevalence of arrhythmia during spontaneous attacks, including OHCA (Table 1). Among the 1317 patients in whom ECG was recorded during spontaneous attack, significant ST-segment elevation and depression was documented in 272 and 121 patients, respectively.

Among the registered patients except for 169 patients (12%, not recorded), angina attacks occurred exclusively at rest in 634 patients (44%), whereas it occurred predominantly at rest but was also induced by effort in 513 patients (36%). In 113 patients (8%), angina attacks were induced only by effort. In 658 patients, typical circadian pattern was identified mostly from midnight to early morning as follows; from midnight to 4 AM (n=160), 4 AM to 8 AM (n=377), 8 AM to noon (n=122), noon to 4 pm (n=36), 4 pm to 8 pm (n=40) and 8 pm to midnight (n=66).

The provocation test was performed during coronary angiography in 1244 patients with either acetylcholine (n=713, 57.3%), ergonovine (n=497, 40.0%), both (n=23, 1.8%), or others (eg, hyperventilation) (n=11, 0.9%). The prevalence of arrhythmic events during provocation test (n=85, 6.8%)

Table 1. Demographic Characteristics of VSA Patients

	Overall	Men	Women	P Value
No. of patients, n (%)	1429 (100)	1090 (76)	339 (24)	<0.001
Age, median (IQR), y	66 (58–73)	66 (58–72)	69 (60–75)	<0.001
Coronary risk factor, n (%)				
Hypertension	666 (47)	511 (47)	155 (46)	0.38
Dyslipidemia	647 (45)	481 (44)	166 (49)	0.07
Diabetes mellitus	233 (16)	186 (17)	47 (14)	0.09
Smoking	848 (59)	781 (72)	67 (20)	<0.001
Family history of IHD, n (%)	168 (12)	118 (11)	50 (15)	0.033
Previous MI, n (%)	91 (6)	81 (7)	10 (3)	0.003
Organic stenosis >50%, n (%)	201 (14)	170 (16)	31 (9)	0.001
ST-segment change during spontaneous attack, n (%)				
ST-elevation	272 (19)	234 (21)	38 (11)	<0.001
ST-depression	121 (8)	83 (8)	38 (11)	0.027
Arrhythmic event during spontaneous attack, n (%)				
PVC	14 (1)	12 (1)	2 (1)	0.32
VT/VF	17 (1)	14 (2)	3 (1)	0.40
AV block	21 (1)	19 (2)	2 (1)	0.09
Bradycardia/sinus pause	28 (2)	20 (2)	8 (2)	0.34
Out-of-hospital cardiac arrest*	35 (2)	30 (3)	5 (1)	0.13

AV indicates atrioventricular; IHD, ischemic heart disease; IQR, interquartile range; MI, myocardial infarction; PVC, premature ventricular contraction; VF, ventricular fibrillation; VSA, vasospastic angina; and VT, ventricular tachycardia.

*Twenty-six patients (male/female, 23/3 patients) were also complicated by nonfatal VT/VF.

was similar with that during spontaneous attack (n=107, 7.5%) (online-only Data Supplement Table 1).

Medical Treatments

In the present study, 1331 patients (93%) were treated with calcium channel blockers (CCBs), either CCBs alone (48%), or combination of CCBs and long-acting nitrates including nicorandil (45%). Most of the patients (n=1162, 81%) were treated with one type of CCB: delayed- or modified-release formulations of first-generation of CCBs in 814 and the second- and third-generation of CCBs with longer plasma half-lives in 348.[18] Antiplatelet agents were used in 669 patients (47%). However, the use of β-blockers was limited to 61 patients (4%) in the present study.

Prognostic Factors of MACE by Multivariate Analysis

During the median follow-up period of 32 months (interquartile range, 17 to 46 months), 19 patients (1.3%) died, in which 6 patients had cardiac death. MACE occurred in 85 patients (5.9%), including myocardial infarction (n=9), hospitalization for unstable angina (n=68) and heart failure (n=4), and appropriate ICD shocks (n=2). Overall 5-year survival rate free from all cause death or MACE was 98% and 91%, respectively (Figure 1). Especially, 5-year survival rate free from nonfatal myocardial infarction was high (99%).
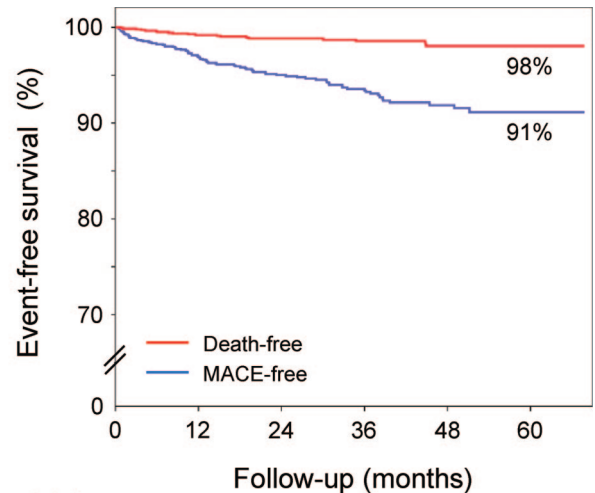
Figure 1. Kaplan–Meier curve for survival (red line) and MACE (blue line) in VSA patients.

Multivariable analysis demonstrated that in addition to the established prognostic factors (smoking, spontaneous attack with ST-segment elevation, multivessel spasm, and significant organic stenosis in major coronary arteries), history of OHCA was significantly correlated with MACE (Table 2). Even when the analysis was limited to the patient without significant coronary stenosis, the survival curve (online-only Data Supplement Figure 2) and the correlated factors were unchanged (online-only Data Supplement Table 2).

Importantly, the rate of cardiac death and nonfatal myocardial infarction in patients in whom medications were reduced or discontinued (8%, 2 of 25 patients) was 10-fold higher than that in the patients with continued medications (0.7%, 10 of 1404 patients, P=0.017).

VSA Patients Who Survived Out-of-Hospital Cardiac Arrest Caused by Coronary Artery Spasm

The present study included 35 VSA patients who survived OHCA as their first manifestation of clinical events in 14 institutes, 7 of which had the emergency care department. In these 7 hospitals, coronary artery spasm was documented in 22 patients (6.0%) of 365 patients resuscitated from OHCA of cardiac origin between April 1, 2003, and December 31, 2008. The OHCA survivors with VSA were characterized by younger age and higher incidence of coronary spasm in the left anterior descending coronary artery as compared with the remaining non-OHCA patients (Table 3). However, the prevalence of significant coronary stenosis was comparable between the 2 groups. Appropriate ICD shocks for ventricular fibrillation (VF) were documented in 2 of the 14 patients with ICD implantation during intensive medical treatment. Sudden cardiac death occurred in 1 patient without an ICD who terminated medication himself before the fatal event. Hospitalization was needed because of nonfatal myocardial infarction (n=1) and unstable angina pectoris (n=3). Despite the comparable incidence of all-cause mortality (Figure 2A),

Table 2.   Correlated Factors for Major Adverse Cardiac Events in VSA Patients

	Univariable Analysis			Multivariable Analysis*		
	HR	95% CI	P Value	HR	95% CI	P Value
Age	0.99	0.97–1.01	0.38			
Men	1.07	0.64–1.79	0.79			
Hypertension	0.90	0.58–1.38	0.62			
Dyslipidemia	1.17	0.76–1.79	0.48			
Diabetes mellitus	1.57	0.94–2.61	0.09	1.39	0.82–2.34	0.22
Smoking	1.96	1.21–3.19	0.006	1.67	1.02–2.73	0.041
Family history of IHD	1.10	0.58–2.06	0.78			
Previous MI	2.19	1.10–4.38	0.026	1.39	0.64–3.02	0.41
Significant organic stenosis	2.28	1.39–3.73	0.001	2.04	1.21–3.44	0.008
ST-elevation during spontaneous attack	1.62	1.01–2.60	0.045	1.77	1.09–2.87	0.022
VT/VF during spontaneous attack†	1.00	0.14–7.18	1.00			
History of OHCA	3.98	1.73–9.13	0.001	3.25	1.39–7.61	0.007
LAD spasm	1.15	0.75–1.77	0.51			
LCx spasm	0.92	0.55–1.53	0.74			
RCA spasm	1.17	0.76–1.78	0.48			
Multivessel spasm	1.45	0.93–2.26	0.10	1.62	1.03–2.56	0.037
Administration of β-blockers	2.34	1.08–5.06	0.032	1.56	0.64–3.79	0.33

CI indicates confidence interval; HR, hazard ratio; IHD, ischemic heart disease; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; OHCA, out-of-hospital cardiac arrest; RCA, right coronary artery; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Analysis was performed on 8 variables including diabetes mellitus, smoking, previous MI, significant organic stenosis, ST-elevation during spontaneous attack, history of OHCA, multivessel spasm, and administration of β-blockers.

†Patients complicated by OHCA were not included.

event-free survival was significantly lower in the OHCA survivors as compared with the non-OHCA patients (72 versus 92% at 5 years, *P*<0.001) (Figure 2B). In subgroup analysis between OHCA survivors who did (n=5) and did not (n=30) have later adverse events, left ventricular ejection fraction and the prevalence of significant coronary stenosis was comparable (online-only Data Supplement Table 3).

Discussion

To the best of our knowledge, the present multicenter study with 1429 patients is the largest cohort of VSA, in which the patients were registered on the basis of standardized criteria by the Japanese Circulation Society.[13] The present study also is characterized by the fact that ≈400 VSA cases with documented spontaneous attacks were included, which enhances the scientific level of the study. In the present study, we were able to demonstrate that VSA patients who survived OHCA are particularly high-risk population, even in the current era with long-acting CCBs.

VSA Patients Who Survived OHCA as a High-Risk Population

In the 2000s, early initiation of cardiopulmonary resuscitation and the widespread use of defibrillation programs have saved many patients with OHCA, making subsequent care of these patients more important than ever.[19] Accumulating evidence indicates that cardiac arrest in the absence of organic heart disease is more common than previously expected.[20] In the autopsy studies in patients with sudden cardiac death, the prevalence of no significant coronary stenosis was higher in

Japanese (26%) than in European populations (4%),[21,22] indicating the potential importance of functional coronary abnormalities in the pathogenesis of sudden cardiac death in Japanese. In the present study, coronary spasm was documented in 6% of the patients resuscitated from OHCA of cardiac origin. The prevalence of vasospasm in OHCA patients appeared to be doubled in comparison with that (3%) reported in the previous study participating 4 French emergency units.[20] Because the racial differences may affect the diagnostic and therapeutic strategies (eg, use of the provocation test), the study with Japanese patients should provide important information for better understanding of the pathogenesis of VSA.

In the present study, the incidence of OHCA in VSA patients was 2.4%, which is 50-fold higher than that (0.05%) in the general Japanese population,[23] indicating that VSA patients, especially those who survived OHCA, are high-risk population. As shown in Figure 2B, event-free survival rate in the OHCA survivors was much lower than in the non-OHCA patients. The event of OHCA and worse clinical outcome may not be coincidental but could be explained in part by severe myocardial ischemia caused by left anterior descending artery spasm (Table 3).[24]

The multivariable analysis also demonstrated that prior history of OHCA events was a novel and significant correlated factor of MACE in VSA patients (Table 2). Although life-threatening arrhythmias may be related to increased disease activity of coronary spasm,[25,26] a potential involvement of an arrhythmic substrate in association with ventricular repolarization abnormalities has been suggested in the previous study.[27,28] In patients with variant angina compli-

Table 3. Demographic Characteristics and Angiographic Findings of VSA Patients With and Those Without Out-of-Hospital Cardiac Arrest

	OHCA (n=35)	Non-OHCA (n=1394)	P Value
Age, median (IQR), y	58 (44–65)	66 (58–73)	<0.001
Men, n (%)	30 (86)	1060 (76)	0.13
Coronary risk factor, n (%)			
Hypertension	13 (37)	653 (47)	0.17
Dyslipidemia	7 (20)	640 (46)	0.002
Diabetes mellitus	4 (11)	229 (16)	0.30
Smoking	24 (69)	824 (59)	0.17
Family history of IHD, n (%)	3 (9)	165 (12)	0.40
Family history of sudden death, n (%)	0 (0)	19 (1)	0.62
Previous MI, n (%)	5 (14)	86 (6)	0.07
Organic stenosis >50%, n (%)	5 (14)	196 (14)	0.56
LAD	4 (11)	112 (8)	0.32
LCx	1 (3)	62 (4)	0.54
RCA	2 (6)	69 (5)	0.53
ST-segment changes during spontaneous attack, n (%)			
ST-elevation	6 (17)	266 (19)	0.49
ST-depression	5 (14)	116 (8)	0.17
Spasm-positive arteries, n (%)*			
LAD	23 (72)	643 (53)	0.025
LCx	11 (34)	306 (25)	0.17
RCA	17 (53)	676 (56)	0.45
Multivessel	13 (41)	361 (30)	0.13

IQR indicates interquartile range; IHD, ischemic heart disease; MI, myocardial infarction; LAD, left anterior descending artery; LCx, left circumflex artery; OHCA, out-of-hospital cardiac arrest; and RCA, right coronary artery.

*Data analyzing 1244 patients (32 OHCA survivors and 1212 non-OHCA patients) who underwent vasospasm provocation test.

cated by cardiac arrest, the prevalence of QT dispersion was significantly higher compared with uncomplicated patients.[27] We also have recently reported that OHCA survivors with coronary spasm demonstrated concomitant idiopathic VF, indicating heterogeneity of the underlying mechanisms.[28]

The association of potentially lethal ischemia-induced ventricular arrhythmias may justify the use of an ICD.[29] Meisel et al[12] reported both the efficacy and limitation of ICD therapy in patients with refractory variant angina. In their 7 patients with variant angina complicated by VF, appropriate ICD shocks were documented in 4 patients, but 1 patient died of electromechanical dissociation even under intensive medical treatment with CCBs. However, in the previous studies with a small number of patients (n=6≈7), the prognosis was favorable in survivors of cardiac arrest caused by coronary spasm who did not receive ICD.[10,11] It remains to be examined in a future multicenter study whether ICD therapy can improve the prognosis of OHCA survivors with coronary spasm.

Importance of Continued Medical Treatment for VSA

After withdrawal of CCB, silent myocardial ischemia with fatal arrhythmias[30] and a rebound phenomenon of the
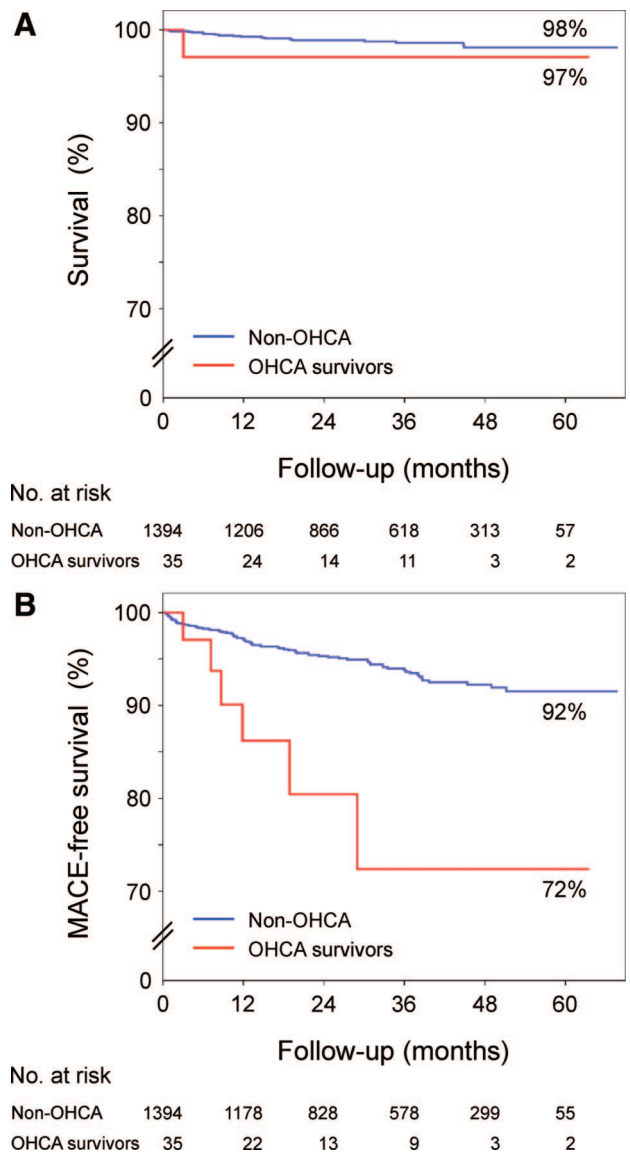

Figure 2. Kaplan–Meier curve for all-cause of death and MACE in VSA patients. **A**, The survival rate was comparable between the VSA patients who survived OHCA (red line, n=35) and those without OHCA (blue line, n=1394) (P=0.30). **B**, MACE-free survival was significantly worse in the VSA patients who survived OHCA (red line, n=35) compared with those without OHCA (blue line, n=1394) (P<0.001). MACE include cardiac death, nonfatal myocardial infarction, hospitalization for heart failure and unstable angina pectoris, and appropriate ICD shocks.

spasm[31,32] could occur. In the present study, the Fisher exact test also demonstrated that the incidence of cardiac death and nonfatal myocardial infarction was significantly increased in patients in whom medications were reduced or discontinued. These findings indicate that medications should not be withdrawn carelessly, even if symptomatic attacks appear to be controlled. Although CCBs remain the mainstay of the current clinical practice, it has been reported that 6-month CCB therapy did not completely normalize coronary vasoconstricting responses to acetylcholine despite the absence of symptomatic angina.[33] Even after 1-year CCB therapy, myocardial fatty acid metabolic images assessed using [123]I-15-(p-iodophenyl)-3-R,S-methyl pentadecanoic acid have been re-

ported to appear abnormal in VSA patients.[34] These findings suggest that there are also limitations of these classes of drug. Recently, the accumulating evidence demonstrated that small GTPase RhoA and its downstream effector Rho-kinase play a central role by increased Ca^{2+} sensitivity of vascular smooth muscle cells in the molecular mechanism of coronary vasospasm in animal models and VSA patients.[35] The inhibition of Rho-kinase with fasudil has been reported to result in the disappearance of coronary vasospastic activity[36] and is a novel therapeutic option that could target specific abnormalities with a resultant remission of VSA.

Changing Characteristics of VSA Patients

In association with the epidemics of obesity and metabolic syndrome, the general population has been rapidly growing older and the Westernization of lifestyle has been progressing, especially in Japan.[37] Thus, the present nationwide multicenter registry study also focuses on the clinical characteristics and outcomes of VSA patients in the current era of the 2000s.

Coronary spasm was most frequently noted in middle-aged men, who otherwise did not exhibit coronary risk factors except for higher prevalence of smoking. In male VSA patients (Table 1), the prevalence of smoking still remains high ($\approx70\%$). The lower incidence of previous myocardial infarction and of organic coronary disease were comparable with the previous report on the clinical characteristics of Japanese patients as compared with Caucasian patients.[38]

Several prognostic studies with a few hundreds of patients were performed in the 1980s. Yasue et al[39] reported that 5-year survival rate free from death or myocardial infarction was 97% and 83% in 245 patients. In general, as reported in the previous comparative study,[38] the prognosis was much worse in a Western population than in a Japanese population.[26,40] In the current era, the clinical outcome of VSA patients appears to be further improved in the 2000s as compared with the 1980s.[26,38–40]

Limitations of the Study

Several limitations should be mentioned for the present study. First, the present study is a retrospective observational study and thus the association found in the present study is not necessarily causal. To address this important issue, we have recently started prospective studies by our Japanese Coronary Spasm Association. Second, the follow-up period was variable, and it is highly possible that many arrhythmic events were missed during the periods of time that the patients were not being monitored. Third, a complex composite primary end point, including ICD shocks, was used in the present study. Appropriate ICD shocks are not certainly a surrogate for sudden cardiac death. Fourth, management decisions were left to the discretion of each attending physician. Fifth, there is no sufficient information available about the date of reduction or discontinuation of medications and thus this variable was not included in the present Cox proportional hazard model. However, despite these limitations, the present findings should merit emphasis for better understanding of the pathogenesis and the long-term prognosis of VSA in the current era.

Conclusions

The present multicenter study by the Japanese Coronary Spasm Association describes the largest cohort of patients with VSA and a cohort who survived cardiac arrest. Especially, VSA patients who survived OHCA are a high-risk population, and the importance of continued medications should be emphasized.

Appendix 1

List of Participating Investigators and Hospitals

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Disclosures

None.

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CLINICAL PERSPECTIVE

Myocardial ischemia is an important cause of out-of-hospital cardiac arrest (OHCA). Coronary artery spasm is a known cause, but there is limited information about the clinical characteristics and long-term prognosis of patients with vasospastic angina (VSA) who survive OHCA. The present multicenter study by the Japanese Coronary Spasm Association describes a large cohort of 1429 patients with VSA and compares 35 who survived OHCA with those without OHCA. Survival rate free from major adverse cardiac events was significantly lower in the OHCA survivors as compared with the non-OHCA patients, including appropriate implantable cardioverter-defibrillator shocks for ventricular fibrillation in 2 patients. Subgroup analysis of all OHCA cases presenting to 7 hospitals suggests a 6% incidence of VSA in survivors of OHCA from cardiac cause. These results indicate that VSA patients who survived OHCA are a high-risk population. Further studies are needed to determine whether implantable cardioverter-defibrillator therapy improves their prognosis.

Circulation
Arrhythmia and Electrophysiology

Clinical Characteristics and Long-Term Prognosis of Vasospastic Angina Patients Who Survived Out-of-Hospital Cardiac Arrest: Multicenter Registry Study of the Japanese Coronary Spasm Association

Yusuke Takagi, Satoshi Yasuda, Ryusuke Tsunoda, Yasuhiro Ogata, Atsushi Seki, Tetsuya Sumiyoshi, Motoyuki Matsui, Toshikazu Goto, Yasuhiko Tanabe, Shozo Sueda, Toshiaki Sato, Satoshi Ogawa, Norifumi Kubo, Shin-ichi Momomura, Hisao Ogawa and Hiroaki Shimokawa

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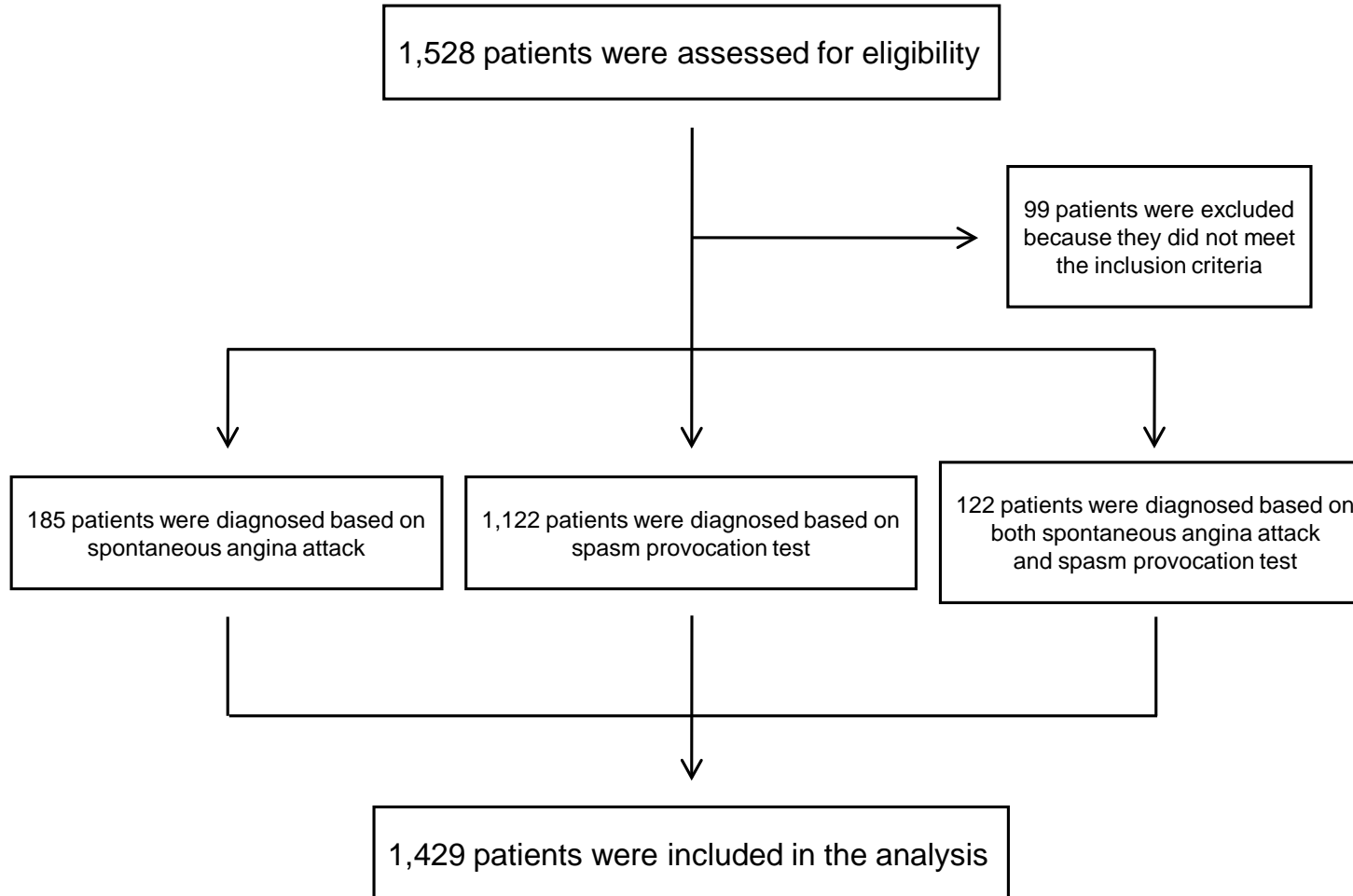
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SUPPLEMENTAL MATERIAL

Supplemental Figure 1. Patient flow diagram

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              ┌─────────────────────────────────────────┐
              │ 1,528 patients were assessed for eligibility │
              └─────────────────────────────────────────┘
                              │
                              │         ┌──────────────────────────┐
                              │────────▶│ 99 patients were excluded │
                              │         │ because they did not meet │
                              │         │    the inclusion criteria │
                              │         └──────────────────────────┘
          ┌───────────────────┼───────────────────┐
          ▼                   ▼                   ▼
┌──────────────────┐ ┌──────────────────┐ ┌──────────────────┐
│ 185 patients were │ │ 1,122 patients were │ │ 122 patients were │
│ diagnosed based on │ │ diagnosed based on │ │ diagnosed based on │
│ spontaneous angina │ │ spasm provocation  │ │ both spontaneous   │
│ attack             │ │ test               │ │ angina attack and  │
│                    │ │                    │ │ spasm provocation  │
│                    │ │                    │ │ test               │
└──────────────────┘ └──────────────────┘ └──────────────────┘
          │                   │                   │
          └───────────────────┼───────────────────┘
                              ▼
              ┌─────────────────────────────────────────┐
              │ 1,429 patients were included in the analysis │
              └─────────────────────────────────────────┘
```

Supplemental Figure 2. Kaplan-Meier curve for survival (red-line) and major adverse cardiac events (MACE) (blue-line) in a total of 1,228 VSA patients without significant coronary stenosis.
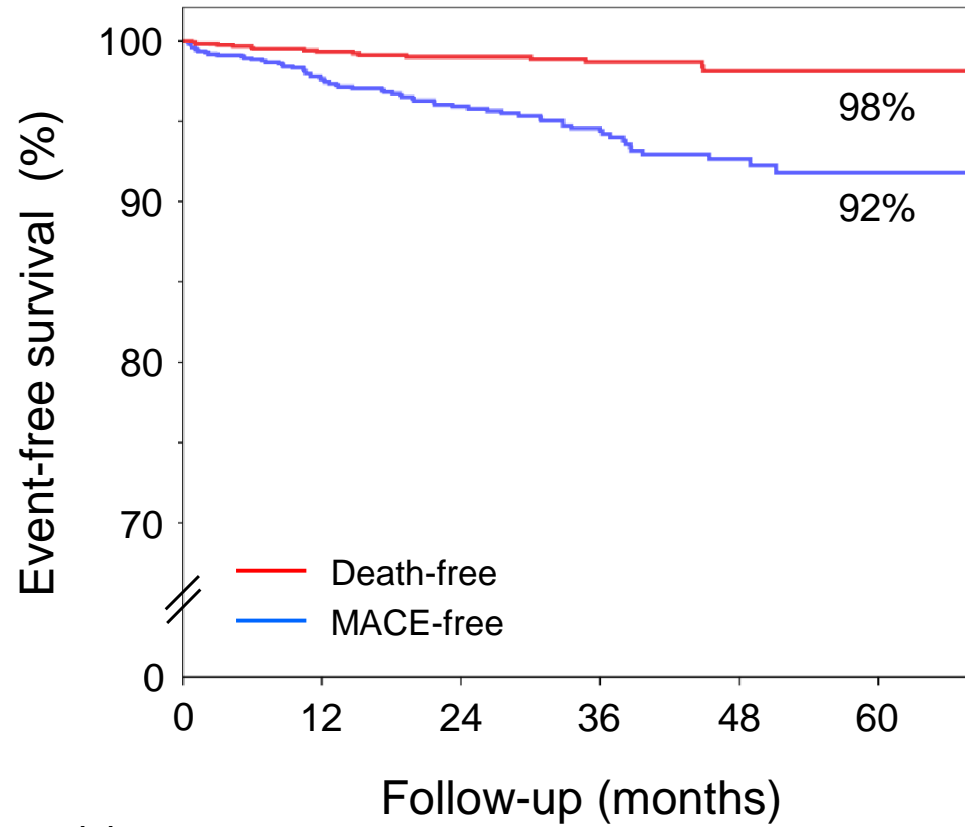
No. at risk						
Death-free	1228	1070	772	557	279	52
MACE-free	1228	1049	744	524	267	50

Supplemental Table 1. Arrhythmic Events during Provocation Tests (n=1,244)

	No. of patients, n (%)
PVC	13 (1.0)
VT/VF	40 (3.2)
AV block	8 (0.6)
Bradycardia/Sinus pause	28 (2.3)
Total	85 (6.8)

AV, atrioventricular; PVC, premature ventricular contraction;
VF, ventricular fibrillation; VT, ventricular tachycardia, including both sustained and non-sustained VT.

Supplemental Table 2. Factors Correlated for Major Adverse Cardiac Events in VSA Patients without Significant Organic Stenosis (n=1,228)

	Univariable analysis			Multivariable analysis *		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.99	0.97 - 1.01	0.36			
Men	0.97	0.55 - 1.70	0.91			
Hypertension	0.90	0.55 - 1.48	0.68			
Dyslipidemia	1.18	0.72 - 1.92	0.52			
Diabetes mellitus	1.39	0.74 - 2.61	0.30			
Smoking	2.35	1.32 - 4.19	0.004	2.12	1.18 - 3.80	0.012
Family history of IHD	1.35	0.69 - 2.64	0.39			
Previous MI	2.90	1.32 - 6.35	0.008	2.21	0.95 - 5.15	0.07
ST elevation during spontaneous attack	1.33	0.76 - 2.35	0.32	1.35	0.75 - 2.43	0.32
VT/VF during spontaneous attack [†]	1.25	0.17 - 9.04	0.82			
History of OHCA	4.85	1.94 - 12.11	0.001	4.22	1.67 - 10.63	0.002
LAD spasm	1.20	0.73 - 1.96	0.47			
LCx spasm	0.84	0.47 - 1.53	0.57			
RCA spasm	1.26	0.77 - 2.05	0.37			
Multivessel spasm	1.51	0.91 - 2.49	0.11	1.45	0.87 – 2.41	0.16
Administration of β-blockers	2.24	0.81 - 6.16	0.12	1.87	0.62 - 5.63	0.27

* Analysis was performed on 6 variables including smoking, previous MI, ST elevation during spontaneous attack, history of OHCA, multivessel spasm and administration of β-blockers.

† Patients complicated by OHCA were not included.

CI, confidence interval; HR, hazard ratio; IHD, ischemic heart disease; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; OHCA; out-of-hospital cardiac arrest; RCA, right coronary artery; VF, ventricular fibrillation; VT, ventricular tachycardia.

Supplemental Table 3. Left Ventricular Function and the Prevalence of Organic Coronary Stenosis in OHCA Survivors with and without MACE after Discharge

	OHCA survivors (n=35)		P value
	(+) MACE (n=5)	(-) MACE (n=30)	
LVEF, median (IQR), %	60 (58, 69)	65 (56, 69)	0.83
LVEF <50%, n (%)	0 (0)	4 (14)	0.45
Organic stenosis >50%, n (%)	1 (17)	4 (14)	0.63
LAD	0 (0)	4 (14)	0.45
LCx	0 (0)	1 (3)	0.83
RCA	1 (17)	1 (3)	0.32

IQR, interquartile range; LVEF, left ventricular ejection fraction.

Appendix 1

List of participating investigators and hospitals

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(47 institutes)