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Clinical implications of provocation tests for coronary artery spasm: safety, arrhythmic complications, and prognostic impact: Multicentre Registry Study of the Japanese Coronary Spasm Association

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Aims Provocation tests of coronary artery spasm are useful for the diagnosis of vasospastic angina (VSA). However, these tests are thought to have a potential risk of arrhythmic complications, including ventricular tachycardia (VT), ventricular fibrillation (VF), and brady-arrhythmias. We aimed to elucidate the safety and the clinical implications of the spasm provocation tests in the nationwide multicentre registry study by the Japanese Coronary Spasm Association.

Methods and results A total of 1244 VSA patients (M/F, 938/306; median 66 years) who underwent the spasm provocation tests were enrolled from 47 institutes. The primary endpoint was defined as major adverse cardiac events (MACEs). The provocation tests were performed with either acetylcholine (ACh, 57%) or ergonovine (40%). During the provocation tests, VT/VF and brady-arrhythmias developed at a rate of 3.2 and 2.7%, respectively. Overall incidence of arrhythmic complications was 6.8%, a comparable incidence of those during spontaneous angina attack (7.0%). Multivariable logistic regression analysis demonstrated that diffuse right coronary artery spasm ($P < 0.01$) and the use of ACh ($P < 0.05$) had a significant correlation with provocation-related VT/VF. During the median follow-up of 32 months, 69 patients (5.5%) reached the primary endpoint. The multivariable Cox proportional hazard model revealed that mixed (focal plus diffuse) type multivessel spasm had an important association with MACEs (adjusted hazard ratio, 2.84; 95% confidence interval, 1.34–6.03; $P < 0.01$), whereas provocation-related arrhythmias did not.

Conclusion The spasm provocation tests have an acceptable level of safety and the evaluation of spasm type may provide useful information for the risk prediction of VSA patients.

Keywords Vasospastic angina • Arrhythmia • Prognosis

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Introduction

Coronary artery spasm is one of the important functional abnormalities of the coronary artery and plays a significant role in the pathogenesis of a wide variety of ischaemic heart disease[1–3] and arrhythmic events.[4] Since Prinzmetal *et al.*[5] first described vasospastic angina (VSA) as a 'variant angina' in 1959, the accumulated evidence revealed several prognostic factors of VSA patients, including smoking, organic coronary stenosis, and multivessel spasm.[6–9] Our previous study with >1400 patients also demonstrated that VSA patients who survived out-of-hospital cardiac arrest (OHCA) are particularly high risk population.[10]

As a useful diagnostic tool for VSA, pharmacological and non-pharmacological provocation tests of coronary spasm during coronary angiography have been established, because coronary spasm develops transiently and it is not so easy to document spontaneous attack in the clinical situation. The provocation tests can also be utilized to evaluate the impairment of coronary vasomotor function including endothelial dysfunction[11,12] and coronary hyperconstricting responses after drug-eluting stent implantation.[13] However, these tests are thought to have a potential risk of serious complications, including ventricular tachycardia (VT), ventricular fibrillation (VF), and brady-arrhythmias, although there has been little knowledge about the clinical implications of arrhythmic complications of these tests except for a few clinical studies[14–16] or anecdotal reports.[17] In addition, the relationship between the angiographic findings, including type of spasm during the provocation tests and the outcomes of VSA patients, remains to be fully examined.

In the present study, we thus aimed to elucidate (i) the incidence and the prognostic impact of arrhythmic complications, especially VT/VF, of the spasm provocation tests and (ii) the correlation between the angiographic findings and patient prognosis in the nationwide multicentre study conducted by the Japanese Coronary Spasm Association.

Methods

The Japanese Coronary Spasm Association was founded in 2006 and currently consists of 75 institutes. The present study was approved by the institutional review boards or ethics committees of all participating institutes.

Study patients

All VSA patients were referred or admitted to the participating institutes and were diagnosed between 1 April 2003 and 31 December 2008.[10] The registration was made between 1 September 2007 and 31 December 2008. The 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 study had been originally planned as a retrospective design. However, the subjects covered in the registration were prospectively expanded for the purpose of increasing study population. The diagnosis of VSA was made based on the spasm provocation tests and/or spontaneous angina attack defined by the Guidelines for Diagnosis and Treatment of Patients with Vasospastic Angina of the Japanese Circulation Society (JCS).[18] The positive diagnosis of the provocation tests was defined as a total or subtotal (>90%) coronary artery narrowing induced by pharmacological [e.g. acetylcholine (Ach) and ergonovine (Erg)] or non-pharmacological (e.g. hyperventilation) challenge during coronary angiography, accompanied by chest pain and/or ischaemic ECG changes. The definition of spontaneous attack was an angina at rest and/or effort, accompanied by a transient ST-segment elevation or depression of >0.1 mV or a newly appearance of negative U-wave on ECG.[18]

Coronary spasm provocation tests

Pharmacological provocation tests of coronary artery spasm were performed with intracoronary injection of ACh or Erg during coronary angiography in accordance with the following procedures.[15,16,18,19] After control coronary angiography, ACh was administered in a stepwise manner into the left coronary artery (LCA) (20–100 μg) and the right coronary artery (RCA) (20–50 μg) over a period of 20 s with a 3–5 min interval between each injection. When Erg was used, it was administrated in a stepwise manner into the LCA (20–60 μg) and RCA (20–60 μg) over a period of 2–5 min.[18] Coronary angiography was performed 1 min after each injection of these agents and when chest pain and/or ischaemic ECG changes were observed. The decisions of selecting agents and whether the LCA or RCA was subjected first were left to the discretion of the physicians. The provocation tests were performed after a washout period of at least 24 h for calcium channel blockers (CCBs) and nitrates.

Data collection

The demographic and clinical data were submitted to a central database system, including age, sex, coronary risk factors, types of angina episodes, circadian distribution of angina attacks, ST-segment changes and arrhythmias during spontaneous attacks, angiographic findings and arrhythmic complications of the spasm provocation tests, medications, and device therapy such as implantable cardioverter defibrillator (ICD). The clinical outcomes during follow-up periods were also collected. Follow-up data were obtained from each participating or cooperating hospital records and patient's regular visits to physicians in the outpatient clinic.

Hypertension, dyslipidaemia and diabetes mellitus were diagnosed based on the guidelines of the Japanese Society of Hypertension, Japan Atherosclerosis Society, and Japan Diabetes Society, respectively.[20–22] Organic coronary stenosis was assessed as either non-significant (25–50% luminal narrowing) or significant (>50% luminal narrowing) by coronary angiography. The types of coronary spasm were classified into focal, diffuse, and mixed type. The focal spasm was defined as a discrete luminal narrowing localized in the major coronary artery, whereas the diffuse spasm was diagnosed when luminal narrowing was observed continuously from the proximal to the distal segment of the coronary artery.[23] The mixed type was defined as the multivessel spasm in which at least one coronary artery had focal spasm and the other had diffuse spasm (*Figure 1*). The degree of coronary vasoconstriction was semi-quantitatively assessed by the visual estimation of angiography and classified into subtotal or total occlusion. Ventricular tachycardia was defined as three or more consecutive premature ventricular contractions (PVCs). In the present study, VT and VF were classified in the same category, and sustained and non-sustained VT were not differentiated. Atrioventricular (AV) block consisted of second- and third-degree AV block. Bradycardia was defined as sinus rhythm with a rate <50 b.p.m.

Endpoints

The primary endpoint was defined as major adverse cardiac events (MACEs), including cardiac death, non-fatal myocardial infarction,

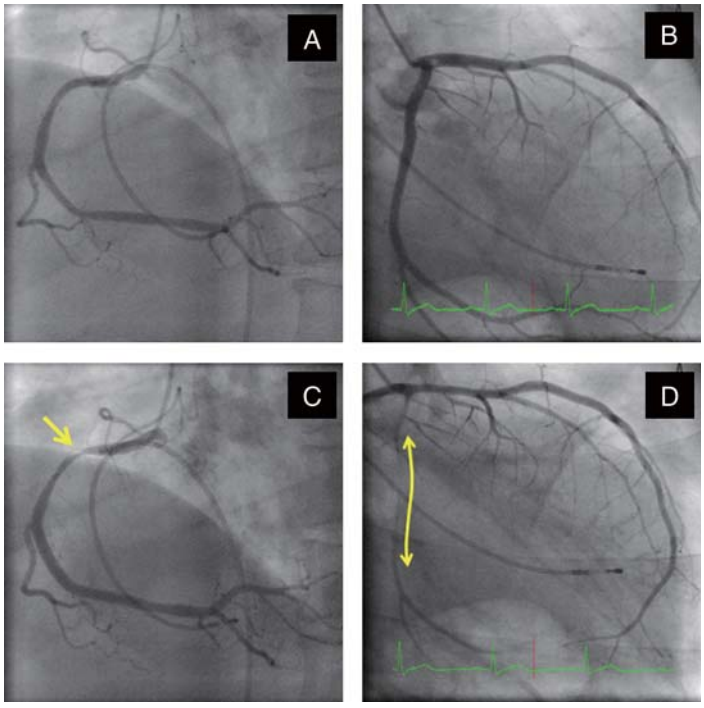

Figure 1 Representative case of mixed-type multivessel spasm. (*A* and *B*) Control angiography showed no significant stenosis in the right and left coronary arteries. (*C*) Intracoronary administration of acetylcholine induced focal spasm in the proximal segment of the right coronary artery (arrow). (*D*) Intracoronary administration of acetylcholine induced diffuse spasm along the left circumflex (line).

hospitalization due to unstable angina pectoris and heart failure, and appropriate ICD shocks during the follow-up period that began at the date of the diagnosis of VSA. The secondary endpoint was all-cause mortality. The definition of these events was previously described.[10]

Statistical analysis

Continuous variables are presented as medians and inter-quartile ranges (IQRs) and categorical variables as percentages. Group comparisons were performed with the Mann–Whitney test for continuous variables, the Chi-square test or Fisher's exact test for categorical variables, and the log-rank test for survival curves. Multivariable analysis of correlated factors of VT/VF during the spasm provocation tests was performed using the logistic regression model. In addition to VT/VF during spontaneous attack, the variables selected based on statistical significance in the group comparison of the patients with and without provocation-related VT/VF were subjected to the forced entry method. Goodness-of-fit for the regression model was examined with the Hosmer–Lemeshow test. Survival free from MACEs and death were analysed by the Kaplan–Meier method. The multivariable Cox proportional hazard model was applied to determine the angiographic variables or arrhythmic complications which correlated with MACEs. Each variable and well-known predictive factors, including age, sex, smoking, previous myocardial infarction, and history of OHCA,[6–8,10] were subjected to the forced entry method. The proportional hazards assumption was examined with the log minus log plot. Subjects with missing data in the selected variables for multivariable analysis were deleted list-wise. The Odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI) were calculated. A two-tailed *P*-value of <0.05 was considered to be statistically significant. The statistical analysis was performed with PASW statistics 18 (SPSS, Inc., Chicago, IL, USA).

Results

Demographic characteristics of the study patients

Among the 1528 patients registered,[10] 284 were excluded because they did not meet the inclusion criteria ($n = 99$) or were diagnosed based on spontaneous attack alone without a provocation test ($n = 185$). Finally, 1244 VSA patients diagnosed based on the spasm provocation tests, including retrospective ($n = 1106$) and prospective populations ($n = 138$), were analysed in this study. The demographic characteristics of the study patients are summarized in *Table 1*. One-fourth of the patients were female ($n = 306$). The prevalence of previous myocardial infarction and significant organic coronary stenosis was relatively low. During spontaneous angina attack, the arrhythmic events were observed in 87 patients (7%), of which 38 patients (3%) were complicated by VT/VF.3

ST-segment changes were documented in 250 patients (ST elevation in 144 and ST depression in 106) during spontaneous angina attack. The demographic characteristics were similar between the patients with and those without ST-segment changes, except that the prevalence of previous myocardial infarction and arrhythmias was higher in patients with ST-segment changes (*Table 1*).

Table 1 Demographic characteristics of vasospastic angina patients who were diagnosed with provocation tests

	Overall	Without ST-segment change	With ST-segment change	*P*-value
No. of patients, *n* (%)	1244 (100)	899 (78)	250 (22)	<0.001
Age, median (IQR), years	66 (58, 73)	66 (58, 73)	65 (57, 73)	0.22
Female, *n* (%)	306 (25)	233 (26)	54 (22)	0.16
Coronary risk factor, *n* (%)				
Hypertension	575 (46)	412 (46)	117 (47)	0.79
Dyslipidaemia	581 (47)	443 (49)	116 (46)	0.42
Diabetes mellitus	212 (17)	154 (17)	49 (20)	0.37
Smoking	733 (59)	532 (59)	156 (62)	0.36
Family history of ischaemic heart disease	145 (12)	113 (13)	28 (11)	0.56
Previous myocardial infarction, *n* (%)	84 (7)	56 (6)	25 (10)	0.039
Organic coronary stenosis, *n* (%)				
Without stenosis	748 (60)	550 (61)	148 (59)	0.57
Non-significant stenosis	316 (25)	222 (25)	63 (25)	0.87
Significant stenosis	180 (15)	127 (14)	39 (16)	0.56
LAD	102 (8)	72 (8)	25 (10)	0.32
LCx	58 (5)	44 (5)	8 (3)	0.25
RCA	67 (5)	43 (5)	17 (7)	0.21
Clinical situation of spontaneous attack, *n* (%)[a]				
Rest	536 (49)	388 (50)	102 (43)	0.046
Effort	105 (10)	72 (9)	26 (11)	0.47
Rest and effort	458 (42)	315 (41)	111 (46)	0.11
Circadian pattern of spontaneous attack, *n* (%)[b]				
Night to morning	461 (83)	329 (86)	107 (76)	0.012
Daytime	143 (26)	87 (23)	48 (34)	0.007
ST-segment change during spontaneous attack, *n* (%)[c]				
ST elevation	144 (13)	—	144 (58)	—
ST depression	106 (9)	—	106 (42)	—
Arrhythmic event during spontaneous attack, *n* (%)	87 (7)	43 (5)	40 (16)	<0.001
PVC	12 (1)	6 (1)	6 (2)	0.028
VT/VF	38 (3)	22 (2)	12 (5)	0.052
AV block	11 (1)	4 (0.4)	7 (3)	0.003
Bradycardia/sinus pause	23 (2)	8 (1)	15 (6)	<0.001
Out-of-hospital cardiac arrest	32 (3)	21 (2)	8 (3)	0.44

[a]Data of situation were available for 1099 patients.
[b]Data of circadian pattern were available for 556 patients.
[c]Data of ST-segment change were available for 1149 patients.

Angiographic findings and arrhythmic complications during spasm provocation tests

The spasm provocation tests were performed with either ACh ($n = 713$), Erg ($n = 497$), both ACh and Erg ($n = 23$), or others (e.g. hyperventilation, $n = 11$). The prevalence of coronary spasm of the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCx) and RCA was 56, 27, and 59%, respectively (*Table 2*). Multivessel spasm was documented in 32% of the patients, whereas the left main trunk spasm was not observed. Diffuse spasm was more frequently observed than focal spasm in each coronary artery. Mixed-type spasm accounted for 20% of the patients with multivessel spasm. The prevalence of coronary spasm in each vessel and the form of coronary vasoconstrictions varied considerably between the patients subjected to ACh and Erg. When compared with the provocation test with ACh, that with Erg revealed a significantly higher incidence of focal and total occlusive spasm. The comparisons of patient characteristics between the two agents are summarized in Supplementary material online, *Table S1*.

During the provocation tests, VT/VF and brady-arrhythmias developed at a rate of 3.2% ($n = 40$) and 2.7% ($n = 34$), respectively (*Table 2*). Overall incidence of arrhythmic complications

Table 2 Angiographic findings and arrhythmic complications during coronary spasm provocation tests

	Overall (n = 1244)	Acetylcholine (n = 713)	Ergonovine (n = 497)	P-value
Spasm-positive artery, n (%)[a]				
LAD	666 (56)	468 (70)	179 (37)	<0.001
Focal/diffuse[b]	253 (40)/375 (60)	140 (32)/298 (68)	108 (63)/63 (37)	<0.001
Subtotal/total	212 (32)/454 (68)	159 (34)/309 (66)	44 (25)/135 (75)	0.021
LCx	317 (27)	222 (33)	88 (18)	<0.001
Focal/diffuse[b]	93 (32)/200 (68)	53 (26)/153 (74)	38 (47)/42 (53)	<0.001
Subtotal/total	115 (36)/202 (64)	90 (40)/132 (60)	19 (22)/69 (78)	<0.002
RCA	693 (59)	389 (58)	279 (58)	0.83
Focal/diffuse[b]	278 (44)/359 (56)	141 (39)/216 (61)	131 (51)/126 (49)	0.005
Subtotal/total	152 (22)/541 (78)	96 (25)/293 (75)	48 (17)/231 (83)	0.021
Multivessel	374 (32)	303 (45)	55 (11)	<0.001
Focal/diffuse/mixed[b]	71 (20)/214 (60)/74 (20)	54 (19)/181 (62)/56 (19)	15 (29)/22 (42)/15 (29)	0.027
Subtotal/total/subtotal and total	68 (18)/188 (50)/118 (32)	52 (17)/155 (51)/96 (32)	13 (24)/30 (54)/12 (22)	0.26
Arrhythmia, n (%)	85 (6.8)	66 (9.3)	16 (3.2)	<0.001
PVC	13 (1.0)	5 (0.7)	8 (1.6)	0.13
VT/VF	40 (3.2)	35 (4.9)	4 (0.8)	<0.001
AV block	8 (0.6)	3 (0.4)	3 (0.6)	0.48
Bradycardia/sinus pause	28 (2.3)	26 (3.6)	2 (0.4)	<0.001

[a]Data of spasm-positive artery were available for 1184 patients.
[b]Data of spasm type of LAD, LCx, RCA, and multivessel were available for 628, 293, 637, and 359 patients, respectively.

during the provocation tests was 6.8%, which was comparable with those during spontaneous angina attack (*Table 1*). The provocation test with ACh had a significantly higher rate of arrhythmic complications compared with Erg (ACh 9.3 vs. Erg 3.2%, $P < 0.001$), which was particularly prominent among the patients with VT/VF (ACh 4.9 vs. Erg 0.8%, $P < 0.001$). The comparisons of demographic characteristics and the angiographic findings between the patients with and those without provocation-related VT/VF are shown in *Table 3*. The patients with provocation-related VT/VF were characterized by a higher proportion of ACh use at the provocation test ($P < 0.001$), female ($P = 0.021$), diffuse RCA spasm ($P = 0.007$), multivessel spasm ($P = 0.023$), and lower prevalence of organic coronary stenosis ($P = 0.023$). The incidence of VT/VF during spontaneous attack tended to be higher in patients with provocation-related VT/VF, although it was not statistically significant. To identify the correlated factors of provocation-related VT/VF, multivariable analysis was performed. The logistic regression analysis demonstrated that ACh use at the provocation test and diffuse RCA spasm were strongly correlated with the occurrence of provocation-related VT/VF (*Table 4*, Model 1). When the variables were limited to patient characteristics, the possible role of gender difference in the occurrence of provocation-related VT/VF was suggested (*Table 4*, Model 2). The risk and the correlated factors of provocation-related VT/VF were also assessed among specific subgroups including patients with and those without ST-segment changes during spontaneous attack and OHCA survivors. The incidence of provocation-related VT/VF was comparable (those with ST changes 4.4% vs. those without ST change 2.9%, $P = 0.23$; OHCA survivors 6.3% vs. patients without OHCA 3.1%, $P = 0.28$), and subgroup-specific predictor could not be identified (see Supplementary material online, *Table S2*).

Medical treatment

For the treatment of VSA, CCBs were used in 1173 patients (94%). Also, long-acting nitrates including nicorandil, statins, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were prescribed in 585 (47%), 417 (34%), and 302 patients (24%), respectively. The use of β-blockers was limited to 59 patients (5%). These medications were comparable between the patients with and those without provocation-related VT/VF, except for the use of antiplatelet agents (63% in patients with VT/VF vs. 46% in those without VT/VF, $P = 0.04$). In 32 patients with a history of OHCA, 14 underwent ICD implantation for the secondary prevention of sudden cardiac death.

Long-term outcomes and correlated factors of MACEs

During the median follow-up period of 32 months (IQR: 17–46 months), 69 patients (5.5%) reached the primary endpoint, including cardiac death in 4, non-fatal myocardial infarction in 7, hospitalization due to unstable angina in 55, and heart failure in 3. Appropriate ICD shocks for VF were documented in 2 out of the 14 OHCA survivors with ICD. All-cause death as the secondary endpoint occurred in 16 (1.3%). The long-term outcomes of the whole patients are shown in *Figure 2A*. The 5-year survival rate free from MACEs and all-cause death was 92 and 98%, respectively. Among 40 patients with provocation-related VT/VF, hospitalization was needed due to unstable angina in 2 (5.0%), whereas neither

Table 3 Demographic and angiographic characteristics of vasospastic angina patients with and without provocation-related ventricular tachycardia/ventricular fibrillation

	With provocation-related VT/VF	Without provocation-related VT/VF	*P*-value
No. of patients, *n* (%)	40 (3)	1204 (97)	<0.001
Age, median (IQR), years	64 (59, 68)	66 (58, 73)	0.15
Female, *n* (%)	16 (40)	290 (24)	0.021
Coronary risk factor, *n* (%)			
Hypertension	19 (48)	556 (46)	0.87
Dyslipidaemia	22 (55)	559 (46)	0.29
Diabetes mellitus	9 (23)	203 (17)	0.35
Smoking	21 (53)	712 (59)	0.40
Previous myocardial infarction, *n* (%)	4 (10)	80 (7)	0.28
Organic coronary stenosis, *n* (%)			
Without stenosis	31 (78)	717 (59)	0.023
Non-significant stenosis	5 (12)	311 (26)	0.06
Significant stenosis	4 (10)	176 (15)	0.41
ST-segment change during spontaneous attack, *n* (%)[a]			
ST elevation	7 (19)	137 (12)	0.17
ST depression	4 (11)	102 (9)	0.45
Arrhythmic event during spontaneous attack, *n* (%)			
PVC	0 (0)	12 (1)	0.67
VT/VF	3 (8)	35 (3)	0.12
Out-of-hospital cardiac arrest, *n* (%)	2 (5)	30 (2)	0.28
Provocation agent, *n* (%)[b]			
ACh/Erg	35 (90)/4 (10)	678 (58)/493 (42)	<0.001
Spasm-positive artery, *n* (%)[c]			
LAD	18 (49)	648 (56)	0.34
Diffuse/focal[d]	11 (69)/5 (31)	364 (60)/248 (41)	0.46
Subtotal/total	6 (33)/12 (67)	206 (32)/442 (68)	0.89
LCx	13 (35)	304 (27)	0.24
Diffuse/focal[d]	10 (77)/3 (23)	190 (68)/90 (32)	0.36
Subtotal/total	5 (38)/8 (62)	110 (36)/194 (64)	0.54
RCA	28 (76)	665 (58)	0.031
Diffuse/focal[d]	22 (81)/5 (19)	337 (55)/273 (45)	0.007
Subtotal/total	4 (14)/24 (86)	148 (22)/517 (78)	0.32
Multivessel	18 (49)	356 (31)	0.023
Diffuse/focal/mixed[d]	11 (64)/3 (18)/3 (18)	203 (59)/68 (20)/71 (21)	0.91
Subtotal/total/subtotal and total	3 (17)/10 (55)/5 (28)	65 (18)/178 (50)/113 (32)	0.90

[a]Data of ST-segment change were available for 1149 patients.
[b]Analysis was performed on 1210 patients who underwent the provocation tests with either ACh or Erg.
[c]Data of the spasm-positive artery were available for 1184 patients.
[d]Data of spasm type of LAD, LCx, RCA, and multivessel were available for 628, 293, 637, and 359 patients, respectively.

other cardiac events nor death occurred. Importantly, the MACE-free survival rate was comparable between patients with and those without provocation-related VT/VF throughout the follow-up period (93 vs. 92% at 5 years, $P = 0.90$) (*Figure 2B*).

The angiographic findings and the arrhythmic complications associated with the primary endpoint at univariable and multivariable analysis are shown in *Table 5*. The multivariable Cox proportional hazard model, in which variables were adjusted for established prognostic factors, including age, sex, smoking, previous myocardial infarction and history of OHCA,[6–8,10] demonstrated that mixed-type multivessel spasm and organic coronary stenosis had a significant correlation with MACEs. The arrhythmic complications during the provocation tests were not significantly correlated with patient prognosis. Even though the endpoints were limited to ischaemia-related events including cardiac death, non-fatal myocardial infarction,

Table 4 Correlated factors for provocation-related ventricular tachycardia/ventricular fibrillation on multivariable analysis

	OR	95% CI	*P*-value
Model 1			
Acetylcholine	4.09	1.56–10.73	0.004
Diffuse RCA spasm	3.02	1.57–5.81	0.001
VT/VF during angina attack	2.21	0.62–7.87	0.22
Female	1.87	0.95–3.67	0.07
Model 2			
Diffuse RCA spasm	3.14	1.54–6.41	0.002
Female	2.01	1.00–4.04	0.049
Without organic stenosis	1.68	0.77–3.67	0.19
Multivessel spasm	1.36	0.67–2.76	0.39

Four variables were subjected to each logistic regression model with the forced entry method.

and hospitalization due to unstable angina, the correlated factors were unchanged (see Supplementary material online, *Table S3*). Kaplan–Meier curves for MACEs in patients with mixed-type multivessel spasm are shown in Supplementary material online, *Figure S1*. Even in patients with ST-segment changes during an angina attack, this type of spasm tended to have a prognostic impact, although statistical significance was not derived.

Discussion

The major findings of the present study were that (i) the use of ACh and diffuse RCA spasm were significantly correlated with the occurrence of VT/VF during the coronary spasm provocation tests and (ii) mixed-type multivessel spasm had a significant prognostic impact on VSA patients, whereas the arrhythmic complications during the provocation tests did not. To the best of our knowledge, this is the first study that demonstrates the incidence and the influencing factors of arrhythmic complications during the spasm provocation tests and overall safety of the tests in the largest scale multicentre study.

Safety of spasm provocation tests and influencing factors of arrhythmic complications

Because coronary spasm is a functional abnormality that develops transiently and the documentation of spontaneous attack is not so easy in the clinical situation, the provocation test of the spasm is useful for the diagnosis of VSA. The first provocation test with Erg during coronary angiography was performed at Cleveland Clinic in 1973.[24] Subsequently, Specchia *et al.*[25] and Yasue *et al.*[26] first reported the usefulness of Erg and ACh for the induction of coronary spasm, respectively. Since then, the pharmacological provocation tests with these two agents have been widely

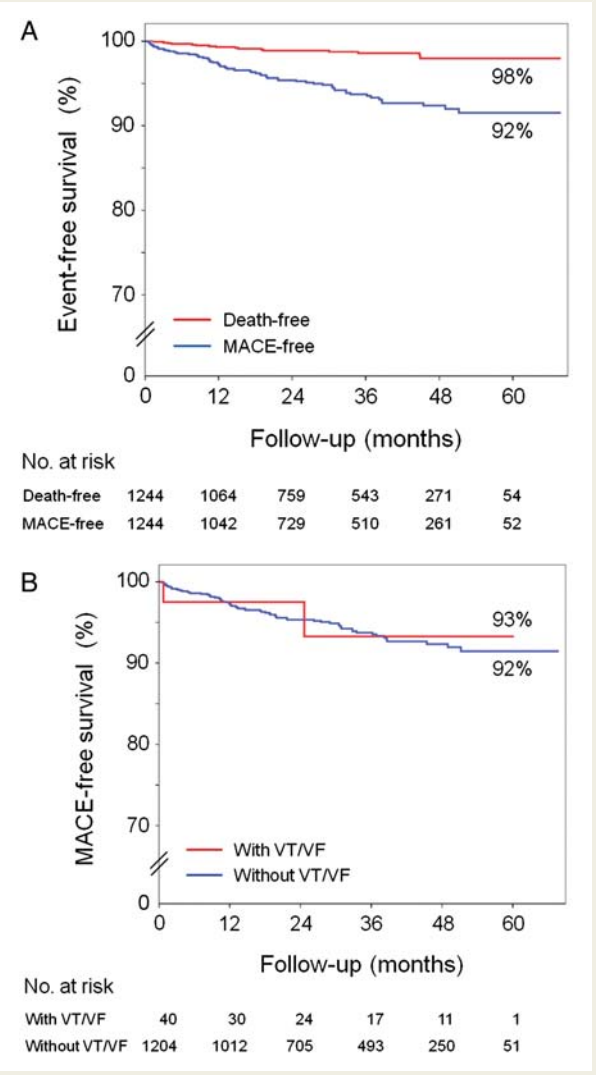

Figure 2 The Kaplan–Meier curve for major adverse cardiac events and survival in vasospastic angina patients after the diagnosis with the provocation tests. (*A*) The Kaplan–Meier curve for survival (red line) and major adverse cardiac event-free survival (blue line) for all the vasospastic angina patients. (*B*) The major adverse cardiac event-free survival rate was comparable between vasospastic angina patients with provocation-related ventricular tachycardia/ventricular fibrillation (red line, $n = 40$) and those without it (blue line, $n = 1204$) ($P = 0.90$).

performed. The ACh challenge can also be utilized to evaluate the impairment of coronary vasomotor function including endothelial dysfunction[11,12] and coronary hyperconstricting responses after drug-eluting stent implantation in patients with organic stenosis.[13] However, along with its usefulness, the safety of the provocation tests remains to be a major concern. The provocation tests are thought to have a potential risk of arrhythmic complications including VT, VF and brady-arrhythmias. In the single-centre trials with hundreds of VSA patients who underwent spasm provocation tests, the incidence of arrhythmic complications was 3.2–5.2% (VT/VF, 3.2–3.7%), while no irreversible complications were noted.[14–16] In the present study, arrhythmic complications

Table 5 Angiographic findings and arrhythmic complications that correlated with major adverse cardiac events

	Univariable analysis			Multivariable analysis[a]		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
LAD spasm	1.28	0.77–2.13	0.35	1.22	0.72–2.05	0.46
LCx spasm	0.99	0.57–1.70	0.96	0.95	0.55–1.64	0.85
RCA spasm	1.28	0.77–2.14	0.34	1.25	0.75–2.08	0.40
Multivessel spasm	1.54	0.94–2.52	0.09	1.47	0.89–2.41	0.13
Type of spasm						
Focal single vessel (reference)	1.00			1.00		
Diffuse single vessel	0.94	0.48–1.85	0.86	0.88	0.45–1.74	0.72
Focal multivessel	0.28	0.04–2.06	0.21	0.27	0.04–1.99	0.20
Diffuse multivessel	1.28	0.64–2.55	0.49	1.15	0.58–2.31	0.69
Mixed multivessel	3.02	1.44–6.36	0.004	2.84	1.34–6.03	0.006
Organic coronary stenosis						
Without stenosis (reference)	1.00			1.00		
Non-significant stenosis	1.82	1.06–3.15	0.031	1.75	1.01–3.04	0.048
Significant stenosis	2.50	1.37–4.58	0.003	2.27	1.23–4.20	0.009
Provocation-related VT/VF	0.92	0.22–3.73	0.90	0.84	0.20–3.43	0.84
Provocation-related brady-arrhythmia	0.05	0.00–25.55	0.34	0.00	0.00–8.22	0.96

[a]Each variable was individually adjusted for age, sex, smoking, previous myocardial infarction, and history of OHCA.
Brady-arrhythmias included AV block, bradycardia, and sinus pause.

occurred in 6.8% (VT/VF, 3.2%) of VSA patients, a comparable incidence of those during spontaneous angina attack. In addition, the Kaplan–Meier curve and the multivariable Cox model demonstrated that arrhythmic complications did not significantly affect long-term prognosis of the VSA patients (*Figure 2B* and *Table 5*). Although the provocation tests should be performed in a setting where appropriate measures for the complications can be prepared, these results suggest that the spasm provocation tests have an acceptable level of safety for the diagnosis of VSA.

To enhance the safety of the provocation tests, the importance of risk identification of arrhythmic complications, especially VT/VF, should be considered. The correlation between RCA spasm and provocation-related ventricular arrhythmias has been previously suggested.[16] In the present study, multivariable logistic regression analysis also demonstrated the novel finding that the use of ACh was significantly correlated with the occurrence of provocation-related VT/VF. Because the accurate awareness of risk factors may lead to an appropriate preparation for serious complications, these findings may provide the safer provocation tests for clinicians.

Diagnostic usefulness and safety between acetylcholine and ergonovine

Although intracoronary injection of ACh and Erg are established diagnostic methods for VSA, it is important to consider their diagnostic usefulness and safety when determining which agent is used. The intracoronary injection of ACh is known to have high sensitivity (90%) and specificity (99%) for the diagnosis of VSA,[27] while there are few reports demonstrating the sensitivity and specificity of Erg. Because of its long half-life, Erg-induced coronary spasm is less likely to resolve spontaneously than ACh-induced spasm and is occasionally refractory to intracoronary vasodilators.[19] In the present study, ACh had a significantly higher incidence of provocation-related VT/VF than Erg. Previous study indicated that baseline QT dispersion was significantly greater in VSA patients complicated by ventricular arrhythmias during the provocation tests.[28] In addition, ACh has non-uniform effects on ventricular endocardial and epicardial action potential, and thus could affect QT dispersion.[29] The potential arrhythmic substrate in some VSA patients and the increased electrical instability due to ACh might be associated with the occurrence of provocation-related VT/VF, although QT dispersion data were not available in the present study.

The slow infusion of provocation agents may possibly reduce the incidence of arrhythmic complications. Several studies demonstrated the provocation procedure with a slower intracoronary ACh than the present study without any complications.[30,31] The correlation between the infusion time of provocation agents and arrhythmic complications should be assessed in future studies, although an excessive slow infusion of ACh may also lead to the underestimation of the prevalence of coronary spasm because of its short half-life of a few seconds.[32]

Our results showed different coronary vasoconstricting responses between ACh and Erg, which could be explained, at least in part, by the difference in patient characteristics (see Supplementary material online, *Table S1*) as well as that in the mechanisms of vasoconstriction between these two agents. Acetylcholine affects both the endothelium and vascular smooth muscle as a cholinergic agonist,

causing endothelium-dependent vasodilatation and endothelium-independent constriction of vascular smooth muscle.[33] Thus, coronary spasm in response to ACh can be regarded as the combined effects of endothelial dysfunction and vascular smooth muscle hyperconstriction.[34] On the other hand, Erg acts via activation of serotonergic receptors, and the Erg-induced coronary vasoconstricting response may predominantly represent endothelium-independent smooth muscle hyperconstriction,[35] although it is conceivable that the effect of Erg is exacerbated by abnormal endothelium. However, since ACh and Erg couple with different receptors followed by different intracellular signalling pathways,[34] the physicians need to be aware that these tests address different kinds of coronary physiology.

Correlation between angiographic findings and patient prognosis

Accumulating evidence indicates that significant organic coronary stenosis is an important prognostic factor of VSA patients.[6–10] In addition, our results revealed the significant impact of non-significant stenosis on patient outcomes (*Table 5*). Life-threatening arrhythmias during spontaneous attack may be related to increased disease activity of VSA.[6–8] We also have recently reported from the multicentre registry study that VSA patients who survived OHCA are at particularly high risk of cardiac events.[10] However, in the present study, arrhythmic complications during the provocation tests were not associated with MACEs, suggesting that the provocation-related arrhythmias do not reflect the severity of this disorder.

Multivessel spasm may cause more extensive myocardial ischaemia and its prognostic impact has been established.[8,10,36] The present study provides the novel finding that mixed-type multivessel spasm had a significant correlation with MACEs, indicating the importance of intensive medical treatments and close follow-up for these patients as well as the clinical usefulness of evaluating spasm type for the risk stratification of future adverse events. Mixed-type spasm may have the potential to predict cardiac events even in patients with ischaemic ECG changes (see Supplementary material online, *Figure S1*), suggesting that the spasm provocation tests may also provide beneficial information for the management of patients in whom VSA had already been diagnosed based on spontaneous attack. Intravascular ultrasound analyses indicated that focal spasm may develop on the background of relatively advanced atherosclerosis,[37,38] and could be associated with rapid progression of organic coronary stenosis.[39,40] In contrast, diffuse spasm could be caused by extensive dysfunction of the coronary artery, and is more frequently documented in particular cases, including spasm-induced myocardial infarction,[41] intractable spasm refractory to conventional treatments,[23] and OHCA.[4] Although the precise mechanisms for the worse clinical outcomes of patients with mixed-type spasm remain to be elucidated, this type of multivessel spasm may share features of both focal and diffuse spasm.

Study limitations

Several limitations should be mentioned for the present study. First, the present study was an observational study and consisted of retrospective and prospective designs. Since the retrospective population accounted for the majority of the study patients, the cause–result relationship was not established. The procedures of provocation tests were not strictly defined in advance of the registration, although the participating physicians performed them in accordance with the aforementioned standard procedures. Furthermore, follow-up periods varied in individual patients and management decisions were left to the discretion of each attending physician. Second, the composite primary endpoint was used. Third, because the JCS guideline recommends performing the provocation tests on both the left and the right coronary arteries, the analysis was performed on the assumption that both coronaries were subjected to the tests. However, due to shortcoming of the patient registration form, it was not necessarily discriminable in some patients that whether the provocation tests were performed on both or one side. This issue could have affected the results of this study. Fourth, the information about arrhythmias was not sufficient. Ventricular tachycardia and VF were included in the same category and the number of patients who required cardioversion for VT/VF during the provocation tests was not available. Since there was no information available regarding the use of temporary pacing[15,26,27] during the provocation tests, the incidence of brady-arrhythmias may have been underestimated. Fifth, the incidence of other complications, including haemodynamic instability and acute myocardial infarction,[14–17] and its prognostic impact were not assessed in the present study. Sixth, since the registry consists of Japanese patients alone in whom the prevalence of VSA and diffuse spasm are higher than in Caucasians,[42,43] the present results may not be extended to all patients worldwide, although the more recent study suggested the comparable prevalence of diffuse spasm.[30] Seventh, the present study only addressed epicardial coronary spasm and the effect of the provocation tests on coronary microcirculation was not assessed. However, despite these limitations, the present findings should merit emphasis for better understanding of the spasm provocation tests and the prognosis of VSA patients.

Conclusions

The present multicentre study by the Japanese Coronary Spasm Association demonstrates the clinical implications of the coronary spasm provocation tests in VSA patients. The spasm provocation tests have an acceptable level of safety, and the evaluation of spasm type may provide useful information for the risk stratification of VSA patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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