Usefulness of Testing for Coronary Artery Spasm and Programmed Ventricular Stimulation in Survivors of Out-of-Hospital Cardiac Arrest

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Background—Optimal therapy for patients resuscitated from out-of-hospital cardiac arrest (OHCA) who are not found to have structural heart disease remains to be established, especially regarding the use of implantable cardioverter-defibrillators. Coronary artery spasm (CAS) and lethal ventricular arrhythmias are important causes of OHCA.

Methods and Results—In 47 consecutive OHCA survivors without structural heart disease who had fully recovered (M/F 44/3, 43±13 years.), we performed dual induction tests, including acetylcholine provocation test first followed by programmed ventricular stimulation after 1 to 2 weeks. Patients with CAS were treated with calcium channel blocker–based antianginal medications; implantable cardioverter-defibrillators were implanted in all patients. The results of the dual induction tests defined 4 groups: CAS alone (n=7), inducible ventricular arrhythmias alone (n=13), both positive (n=24), and both negative (n=3). During a median follow-up period of 38 months, ventricular fibrillation recurred in all groups except the both-negative group. Of the 16 patients with a type I Brugada ECG, 2 had CAS alone, 8 had ventricular arrhythmias alone, and 6 had both positive. No ventricular fibrillation episodes were observed in the CAS-alone patients who did not also have Brugada syndrome. Kaplan–Meier analysis showed that the CAS-alone group was at lower risk for OHCA recurrence as compared with the Brugada syndrome group (log-rank test; P=0.036).

Conclusions—Among OHCA survivors without structural heart disease, provokable CAS and ventricular arrhythmias are common and can be seen in Brugada syndrome. CAS alone without Brugada syndrome who are treated for CAS may be a lower-risk group. **(*Circ Arrhythm Electrophysiol*. 2016;9:e003798. DOI: 10.1161/CIRCEP.115.003798)**

Key Words: angina ■ arrhythmia ■ heart arrest ■ vasospasm

Out-of-hospital cardiac arrest (OHCA) is an important public health problem. The survival rate from OHCA has been increasing in association with widespread use of automatic external defibrillator and educational campaigns on the importance of bystander's cardiopulmonary resuscitation.[1,2] Importantly, among OHCA survivors, a considerable number of patients have no apparent organic heart disease (eg, acute coronary syndrome, cardiomyopathy, myocarditis, pulmonary embolism, and aortic disease), indicating an involvement of functional cardiac disorder(s) in the pathogenesis of OHCA.[3] Among the possible functional causes of OHCA, coronary artery spasm (CAS) and lethal ventricular arrhythmias (VAs), such as Brugada syndrome, long QT syndromes (LQTS), and idiopathic ventricular fibrillation (VF), are major causes of the catastrophe.[4–6] Furthermore, we have recently demonstrated that patients surviving OHCA without organic heart disease are heterogeneous in the pathogenesis of OHCA, suggesting the importance of identification of the presence or absence of those functional disorders by dual induction tests.[7]

The implantable cardioverter-defibrillator (ICD) has become an established device for secondary prevention of sudden cardiac death (SCD) because of lethal VAs.[8] However, it remains as an important unsolved clinical issue whether ICD should be indicated for all patients with OHCA, regardless of the underlying mechanisms involved.[9] In particular, the indication of ICD for the secondary prevention of lethal VAs because of CAS is controversial because CAS could be effectively suppressed by optical medications with calcium channel blockers (CCBs).[10–13]

In the present study, we, thus, examined the long-term prognosis of patients with OHCA classified based on the results of the dual induction tests for CAS and lethal VAs and evaluated the necessity of ICD by the underlying mechanisms involved.

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WHAT IS KNOWN

- A considerable number of OHCA survivors have no apparent structural heart disease.
- Although the pathogenesis of OHCA without structural heart disease is heterogeneous, CAS and lethal VAs are important causes.

WHAT THE STUDY ADDS

- Testing for CAS and inducible VAs identified one or both of these findings in the vast majority of these OHCA survivors who do not have structural heart disease, including patients with ECG manifestations of Brugada syndrome.
- CAS-alone without Brugada syndrome who are treated for CAS may be a lower risk group for recurrence.

Methods

The present study was a prospective, nonrandomized, single-center study and was conducted following the ethical principles in the Declaration of Helsinki. The study protocol was approved by the Ethical Committee of Tohoku University (UMIN000008708), and informed consent was given by each patient.

Study Population

Between December 2004 and September 2014, we enrolled 47 consecutive patients surviving OHCA without organic heart disease who had fully recovered. The diagnosis of organic heart disease was made by physical examination, laboratory tests, 12-lead ECG, chest x-ray, 2-dimensional and color-flow Doppler echocardiography, left ventriculography, and coronary angiography. In the present study, all the patients fulfilled the following criteria, defined by Myerburg et al,[4] including (1) documented VF or sustained rapid ventricular tachycardia (VT), (2) absence of a previous history of heart diseases, (3) normal left ventricular ejection fraction and no wall motion abnormality, (4) absence of significant coronary artery stenosis (American Heart Association/American College of Cardiology classification ≥75%), and (5) absence of identifiable or reversible cause of lethal VAs (eg, electrolyte disturbances, metabolic disturbances, and intoxications/drugs). Because they had fully recovered without neurological sequelae, all of them were able to achieve full rehabilitation after discharge. All available tests in the daily practice (eg, physical examination, laboratory tests, 12-lead ECG, chest x-ray, 2-dimensional and color-flow Doppler echocardiography, left ventriculography, and coronary angiography) were performed before the dual induction tests to identify the underlying cause(s) of OHCA in each patient, and only the patients with suspected CAS and ventricular fibrillation were enrolled in the present study.

Dual Induction Tests for CAS and Ventricular Fibrillation

Induction test for CAS with intracoronary acetylcholine (ACh) was performed at a median 19.5 days after the onset of OHCA. The protocol of ACh provocation test was reported previously.[14] Briefly, ACh was administered into the coronary artery in a cumulative manner (20, 50, and 100 μg), with careful monitoring of arterial pressure and 12-lead ECG and serial coronary angiograms at 1-minute intervals. To determine whether multivessel CAS would develop, we first performed ACh provocation test for the left coronary artery in a cumulative manner (20, 50, and 100 μg). If the test for the left coronary artery was negative or ACh-induced spasms in the left coronary artery resolved spontaneously, we then injected ACh into the right coronary artery in a cumulative manner (20 and 50 μg). Significant CAS was defined, based on the Guidelines by the Japanese Circulation Society,[15] as the development of >90% stenosis accompanied by chest pain or ischemic ECG changes (Figure 1A and 1B). When a significant CAS was induced, 5 mg of isosorbide dinitrate was injected into the responsible coronary artery.

We performed the electrophysiological study for VF induction at a median 8 days after the ACh provocation test (Figure 1C). All patients with positive ACh provocation test were treated with CCBs for at least 1 week before the electrophysiological study for VF. The programed stimulation protocol included a minimum of 2 basic pacing cycle lengths (600 and 400 ms) with single, double, or triple extrastimulation at the right ventricular apex and outflow.[16] If VF was not induced, the same protocol was repeated under isoproterenol stimulation or pacing in the right ventricular outflow.[16] When the patients had a Brugada-like ECG pattern, they additionally underwent drug challenge test using intravenous pilsicainide (1 mg/kg) to diagnose Brugada syndrome.[17] Brugada syndrome was diagnosed when a Brugada type I ECG, characterized by coved ST-segment elevation (≥0.2 mV) and a negative T wave in >1 right precordial lead (V_1–V_3), was found at baseline or pilsicainide challenge test.[5] Early repolarization ECG pattern was defined as an elevation of the QRS-ST junction of at least 1 mm above the baseline level in at least 2 leads.[18]

Follow-Up and End Points

All patients enrolled in the present study underwent ICD implantation, regardless of the results of the dual induction tests (Figure 1D), and were prospectively followed-up. The follow-up period was counted from insertion of an ICD. Appropriate therapy of ICD was defined as antitachycardia or defibrillation treatment for VAs that had not terminated spontaneously. Appropriate ICD therapy and diagnosis of arrhythmia were evaluated from ECG episodes analyzed by 2 specialists of arrhythmias.

Thirty-one patients in whom CAS was induced by ACh provocation test were treated with CCBs and 2 of them with additional long-acting nitrate. Adherence to the prescribed medications was evaluated by medical interview at each clinic visit. Although cessation or addition of prescriptions was left to the discretion of an individual physician, those changes were described in outpatient records and reviewed subsequently. Study end point was the recurrence of VF during a follow-up period.

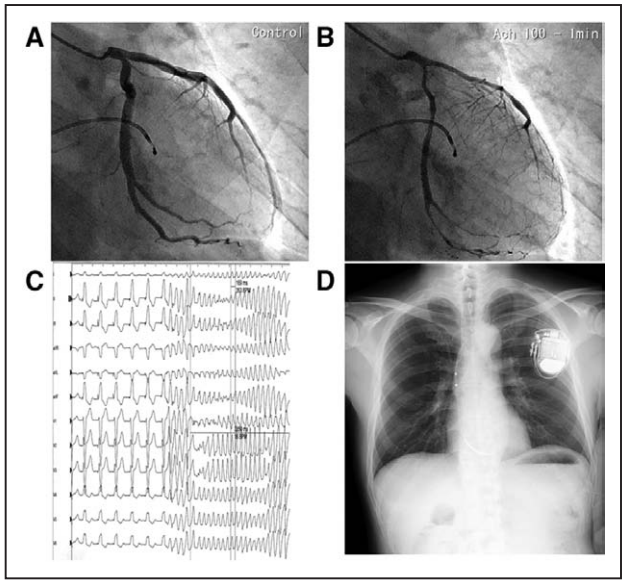

Figure 1. A representative case in the both-positive group by the dual induction tests. **A**, Coronary angiogram before spasm provocation test. **B**, Coronary artery spasm induced by intracoronary acetylcholine. **C**, Ventricular fibrillation induced by electrophysiological study. **D**, Subsequent implantation of implantable cardioverter-defibrillator.

Table 1. Baseline Characteristics of the Patients in the 5 Groups

	Overall (n=47)	CAS Alone (n=5)	VAs Alone (n=5)	Both Positive (n=18)	Both Negative (n=3)	Brugada Syndrome (n=16)	*P* Value
Age, y	43.3±13.9	56.4±11.6	30.8±5.5	43.9±14.6	44.3±15.2	42.1±12.7	0.068
Male, n (%)	44 (94)	5 (100)	5 (100)	16 (89)	3 (100)	15 (94)	0.835
BMI, kg/m^2	21.9±2.9	23.3±4.4	20.3±1.6	22.1±2.6	23.8±6.0	21.4±2.4	0.549
Coronary risk factors							
Hypertension, n (%)	8 (17)	1 (20)	1 (20)	5 (28)	0 (0)	1 (6)	0.483
Dyslipidemia, n (%)	15 (32)	3 (60)	0 (0)	6 (33)	2 (67)	4 (25)	0.185
Diabetes mellitus, n (%)	2 (4)	0 (0)	0 (0)	0 (0)	2 (67)	4 (25)	0.106
Current smoking, n (%)	27 (57)	4 (80)	2 (40)	10 (56)	0 (0)	11 (73)	0.120
Familial history of SCD, n (%)	4 (9)	0 (0)	1 (20)	1 (6)	0 (0)	2 (13)	0.700
Symptoms before OHCA, n (%)	17 (36)	3 (60)	1 (20)	9 (50)	1 (33)	3 (19)	0.249
Chest pain, n (%)	13 (28)	3 (60)	1 (20)	8 (44)	1 (33)	0 (0)	0.022
Palpitation, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Syncope, n (%)	5 (11)	0 (0)	0 (0)	2 (0)	1 (33)	2 (13)	0.578
Presyncope, n (%)	2 (4)	0 (0)	0 (0)	1 (6)	0 (0)	1 (6)	0.937
Situation at OHCA							
Rest onset, n (%)	29 (62)	3 (60)	3 (60)	7 (39)	3 (100)	13 (81)	0.077
Effort onset, n (%)	18 (38)	2 (40)	2 (40)	11 (61)	0 (0)	3 (19)	0.077
ECG findings							
ER ECG pattern, n (%)	10 (21)	1 (20)	1 (20)	5 (28)	1 (33)	2 (13)	0.834
QTc, ms	406.7±28.7	393.2±25.9	389.2±20.9	411.8±26.9	375.3±16.9	416.6±29.8	0.040
AF, n (%)	9 (19)	1 (20)	2 (40)	5 (28)	1 (33)	0 (0)	0.168
Positive for LP, n (%)	25 (53)	2 (40)	0 (0)	8 (44)	2 (67)	13 (81)	0.026
Echocardiography							
LVEF, %	66.8±6.8	68.8±7.0	63.7±8.0	66.6±6.6	72.9±4.5	66.1±7.2	0.566
LVDd, mm	46.9±3.6	46.6±3.7	47.7±2.6	47.3±3.4	43.9±2.9	46.9±4.2	0.626
Laboratory data							
Sodium, mEq/L	140.8±2.7	140.2±2.2	140.6±1.5	141.7±3.0	141.0±3.6	140.1±2.6	0.673
Potassium, mEq/L	3.94±0.55	4.12±0.58	4.12±0.27	3.87±0.61	4.30±0.72	3.84±0.52	0.781
Chloride, mEq/L	103.5±2.8	103.0±4.5	104.4±1.5	103.3±3.0	103.7±2.5	103.6±2.6	0.212
Cr, mg/dL	0.88±0.24	0.68±0.19	0.77±0.98	0.88±0.24	0.93±0.15	0.95±0.27	0.458
Hb, g/dL	14.0±1.7	13.2±1.7	13.8±1.0	14.5±1.4	12.4±4.0	14.0±1.5	0.458
TC, mg/dL	179.9±31.2	183.0±39.2	178.8±21.0	174.8±31.1	208.3±19.9	179.7±33.3	0.560
LDL, mg/dL	113.7±30.0	120.8±51.7	104.8±10.8	110.2±28.2	147.3±22.7	111.9±27.4	0.366
HDL, mg/dL	43.8±14.1	35.0±7.2	48.8±19.6	44.9±15.1	34.3±5.5	45.6±13.1	0.321
TG, mg/dL	153.1±95.7	230.0±192.5	139.4±116.3	125.5±65.7	149.3±37.6	169.9±92.4	0.402
HbA1c, %	5.65±0.51	5.6±0.2	5.5±0.3	5.6±0.4	6.0±0.5	5.7±0.7	0.683
BNP, pg/mL, median (IQR)	13.2 (5.8–47.4)	34.9 (16.0–58.1)	5.8 (5.8–11.6)	27.6 (10.7–111.2)	20.4 (5.8–193.0)	8.1 (5.8–25.0)	0.047
hs-CRP, mg/dL, median (IQR)	0.11 (0.03–0.21)	0.06 (0.02–0.17)	0.03 (0.02–0.14)	0.11 (0.03–0.79)	0.23 (0.12–0.36)	0.10 (0.03–0.35)	0.306
Medications							
CCBs, n (%)	31 (66)	5 (100)	0 (0)	18 (100)	0 (0)	8 (50)	0.000

(*Continued*)

Table 1. Continued

	Overall (n=47)	CAS Alone (n=5)	VAs Alone (n=5)	Both Positive (n=18)	Both Negative (n=3)	Brugada Syndrome (n=16)	*P* Value
Benidipine, n (%)	23 (49)	3 (60)	0 (0)	13 (72)	0 (0)	7 (88)	
Diltiazem, n (%)	7 (15)	1 (20)	0 (0)	5 (28)	0 (0)	1 (12)	
Antiarrhythmic agents, n (%)	3 (6)	0 (0)	1 (20)	1 (6)	1 (33)	0 (0)	0.156

Results are expressed as mean±SD, median (IQR) or number (%). AF indicates atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blocker; Cr, creatinine; ECG, electrocardiogram; ER, early repolarization; Hb, hemoglobin; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; LP, late potential; LVDd, left ventricular dimension diastolic; LVEF, left ventricular ejection fraction; OHCA, out-of-hospital cardiac arrest; QTc, corrected QT interval; SCD, sudden cardiac death; SD, standard deviation; TC, total cholesterol; TG, triglyceride; VAs, ventricular arrhythmias; and VF, ventricular fibrillation.

Statistical Analysis

Continuous variables are presented as means±standard deviations or medians and interquartile ranges and categorical variables as numerals and percentages. Group comparisons were performed with Kruskal–Wallis test for multiple continuous variables and Mann–Whitney U test. Chi-square test was used for categorical variables. Survival free from VF recurrence was analyzed by Kaplan–Meier method, and comparison between groups was performed using log-rank tests. *P* values <0.05 were considered to be statistically significant. The statistical analysis was performed with SPSS statistics 20 (IBM Corp, Armonk, NY).

Results

Characteristics of OHCA Survivors Classified by the Dual Induction Tests

Forty-seven OHCA survivors without organic heart diseases (47±13 years, M/F 44/3) underwent staged induction tests for CAS first and then for VAs. Overall patient characteristics are summarized in Table 1. Only 4 patients had a familial history of SCD, whereas the majority had developed OHCA sporadically. In ≈40% of them, OHCA occurred during exertion. Most of them developed VF during mild exertion, whereas in 3 cases during hard exercise, including baseball, soccer, and marathon. However, exercise challenge testing performed at a later period did not reproduce VAs in those patients. There was no patient with overt LQTS defined by a prolonged corrected QT interval (>450 ms for men or >460 ms for women) at rest. On the other hand, a Brugada-like ECG pattern and an early repolarization ECG pattern were observed in 16 and 10 patients, respectively. All patients had no previous history of heart disease or structural abnormality with 2-dimensional and color-flow Doppler echocardiography. Moreover, 25 patients (53%) underwent cardiac magnetic resonance imaging with no finding of arrhythmogenic right ventricular cardiomyopathy or subclinical myocarditis.

Based on the results of the dual induction tests, all the subjects were classified into the following 4 groups: CAS-alone (n=7, 15%), VAs-alone (n=13, 28%), both-positive (n=24, 51%), and both-negative (n=3, 6%) groups (Figure 2A). Among the 4 groups, there was no statistical difference in almost all of the clinical characteristics, except for the prevalence of diabetes mellitus (Table in the Data Supplement). Furthermore, no significant difference was noted in the factors that could influence the development of VF, such as corrected QT interval, late potential, familial history of SCD, or serum levels of electrolytes (Table in the Data Supplement). More than 90% of the patients were positive for at least 1 test, and the positive rates for CAS and VAs were 66% and 78%, respectively. Table 2 shows angiographic findings and arrhythmic complications during ACh provocation tests for the patients with CAS. As compared with the both-positive group, diffuse spasm tended to be more common and occlusive spasm was induced more frequently in the CAS-alone group. However, in only one case with both positive results, VF occurred and a subsequent cardioversion was needed during ACh provocation test.

Long-Term Prognosis of the 4 Groups Based on the Dual Induction Tests

During a median follow-up period of 38 months, 15 recurrent VF episodes occurred, of which 13 cases were terminated by ICD shocks and the remaining 2 terminated spontaneously. Those recurrent VF episodes were identified by a review of ECGs stored in ICD, and there was no episode of inadequate ICD firing. All 13 patients who experienced ICD shocks were successfully resuscitated and are still alive. The number of recurrent VF was 1 in the CAS-alone group, 7 in the VAs-alone group, 7 in the both-positive group, and none in the both-negative group. There were no significant differences in VF recurrence among the 4 groups (Figure 2B). The review of medication adherence for all patients with recurrent VF found that the adherence was excellent in them. Additionally, no reproducible VF induced by exertion, which is characteristic of catecholaminergic polymorphic VT, was noted throughout the follow-up period.

Long-Term Prognosis According to the Presence or Absence of Brugada Syndrome

Sixteen patients (34% of all patients) presented with a type I Brugada ECG at baseline or during pilsicainide challenge test. When those patients with Brugada syndrome were separated as a different group, the remaining 31 patients without Brugada-like ECG pattern were classified as follows: CAS-alone in 5 (11%), VAs-alone in 5 (11%), both-positive in 18 (38%), and both-negative in 3 (6%; Figure 3A). As shown in Table 1, statistically significant difference was noted in few demographic and clinical characteristics among the 5 groups. Importantly, no VF episodes were noted in the patients with CAS alone and without Brugada syndrome throughout the follow-up period. They had significantly better long-term prognosis as compared with those with Brugada syndrome

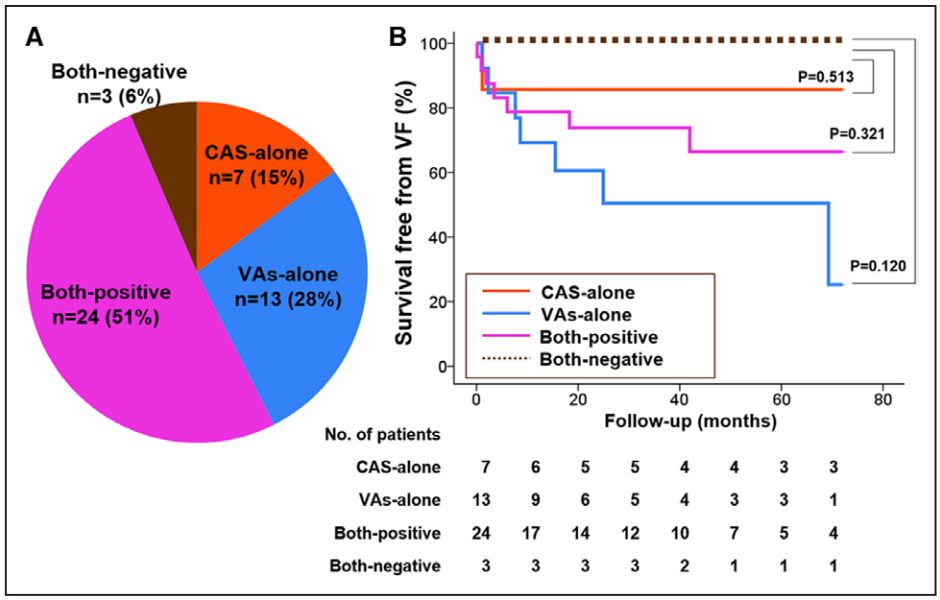

Figure 2. Classification of out-of-hospital cardiac arrest (OHCA) survivors by the dual induction tests. **A**, Distribution of patients classified by dual induction tests. **B**, Kaplan–Meier curves for sudden death according to the groups classified by dual induction tests. CAS indicates coronary artery spasm; VAs, ventricular arrhythmias; and VF, ventricular fibrillation.

(log-rank test; *P*=0.036), whereas its Bonferroni adjusted *P* value for multiple comparisons was 0.108 (Figure 3B).

On the contrary, 16 patients with Brugada syndrome were classified by the dual induction test as follows: CAS-alone (n=2, 12%), VAs-alone (n=8, 50%), both-positive (n=6, 38%), and both-negative (n=0, 0%; Figure 4A). In the patients with Brugada syndrome, recurrent VF was noted in all subgroups (Figure 4B). In particular, a male patient with Brugada syndrome and CAS alone developed sudden death because of recurrent VF without a cautionary chest pain or preceding ischemic ECG changes, although he was treated with antianginal agents, including CCBs (Figure 5). Because the role of electrophysiological testing for predicting OHCA remains controversial in Brugada syndrome,[19] dual induction tests might be less reliable in patients with the disorder.

Discussion

The major findings of the present study were that (1) among OHCA survivors, there was a distinct heterogeneity in the prevalence of CAS and Vas, and half of them had both CAS and VAs, (2) Brugada-like ECG pattern was a significant predictor of recurrent VF, and (3) OHCA survivors with CAS alone and without Brugada syndrome had no episode of recurrent VF. To the best of our knowledge, this is the

Table 2. Result of Acetylcholine Provocation Test for the Patients With Coronary Artery Spasm

	Overall (n=31)	CAS Alone (n=7)	Both Positive (n=24)	*P* Value
Spasm type, n (%)				
Focal	8 (26)	1 (14)	7 (29)	0.429
Diffuse	22 (71)	6 (86)	16 (67)	0.329
Occlusive	5 (16)	3 (43)	2 (8)	0.029
Spasm-positive artery, n (%)				
Left anterior descending artery	26 (84)	7 (100)	19 (79)	0.187
Left circumflex artery	16 (52)	4 (57)	12 (50)	0.739
Right coronary artery	9 (29)	1 (14)	8 (33)	0.329
Multivessels	17 (55)	5 (71)	12 (50)	0.316
Arrhythmia, n (%)				
Paf	3 (10)	1 (14)	2 (8)	0.639
Bradycardia	5 (16)	0 (0)	5 (21)	0.187
PVC	3 (10)	1 (14)	2 (8)	0.639
VA	1 (3)	0 (0)	1 (4)	0.583

Results are expressed as number (%). CAS indicates coronary artery spasm; Paf, paroxysmal atrial fibrillation; PVC, premature ventricular contraction; and VA, ventricular arrhythmia.

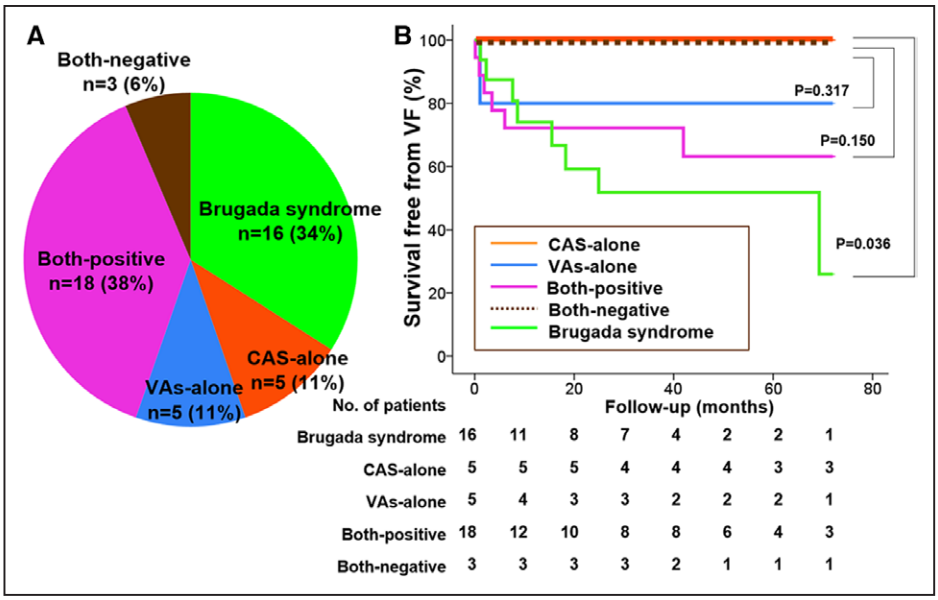

Figure 3. Classification of out-of-hospital cardiac arrest (OHCA) survivors when analyzing the patients with Brugada syndrome as a separate group. **A**, Distribution of patients when the patients with Brugada syndrome were separated as a different group. **B**, Kaplan–Meier curves for sudden death by the groups classified by the presence or absence of Brugada syndrome and by the dual induction tests. CAS indicates coronary artery spasm; VAs, ventricular arrhythmias; and VF, ventricular fibrillation.

first study demonstrating that among OHCA survivors, those with CAS alone and without Brugada syndrome in the dual induction tests may be at low risk for recurrent sudden death and subsequent ICD firing.

Heterogeneity in the Pathogenesis of OHCA Without Organic Heart Disease

The number of OHCA is 295 000 per year in the United States, of which 23% have an initial rhythm of VAs, including VF and VT or other shockable rhythm.[20] Although organic heart disease (eg, acute myocardial infarction) is a major cause of OHCA, lethal VAs could occur in patients without organic heart disease,[21] and both CAS and lethal VAs have been considered as major causes of the catastrophe.[4–6] We have previously demonstrated the heterogeneity in the pathogenesis of OHCA without organic heart disease and the importance of the dual induction tests for both CAS and VF.[7] Indeed, in the present study, we were able to identify all the 4 groups among OHCA survivors by the dual induction tests. Importantly, among the 47 OHCA survivors, including 16 with Brugada syndrome, only 3 were negative for both of them, and the remaining 44 were positive for at least one of them. Furthermore, half of the OHCA survivors had both CAS and lethal VAs, in whom VF was still induced by electrophysiological study, despite the treatment of CAS with CCBs. These findings indicate that electrophysiological abnormalities coexist

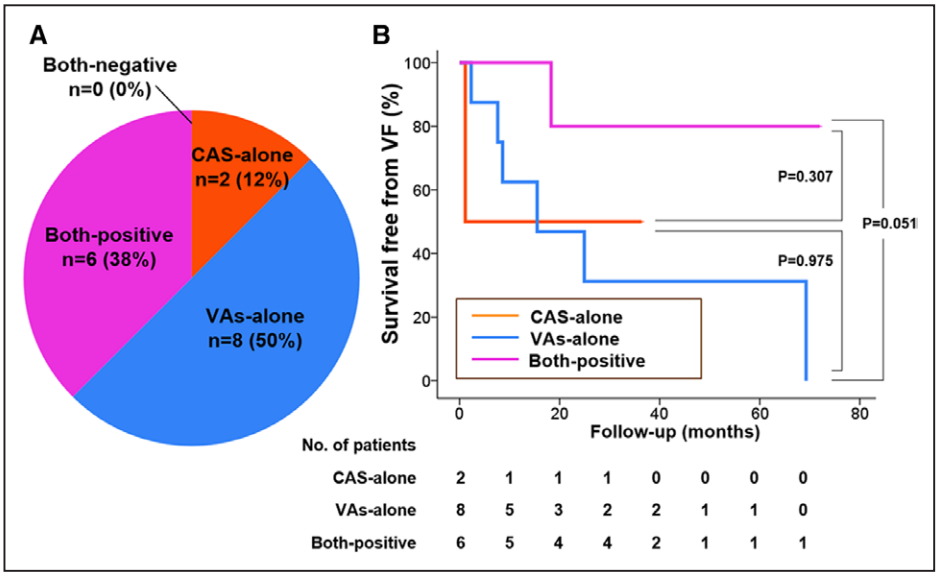

Figure 4. Dual induction tests of out-of-hospital cardiac arrest (OHCA) survivors with Brugada syndrome. **A**, Distribution of patients with Brugada syndrome by dual induction tests. **B**, Kaplan–Meier curves for sudden death by the groups classified by dual induction tests in patients with Brugada syndrome. CAS indicates coronary artery spasm; VAs, ventricular arrhythmias; and VF, ventricular fibrillation.

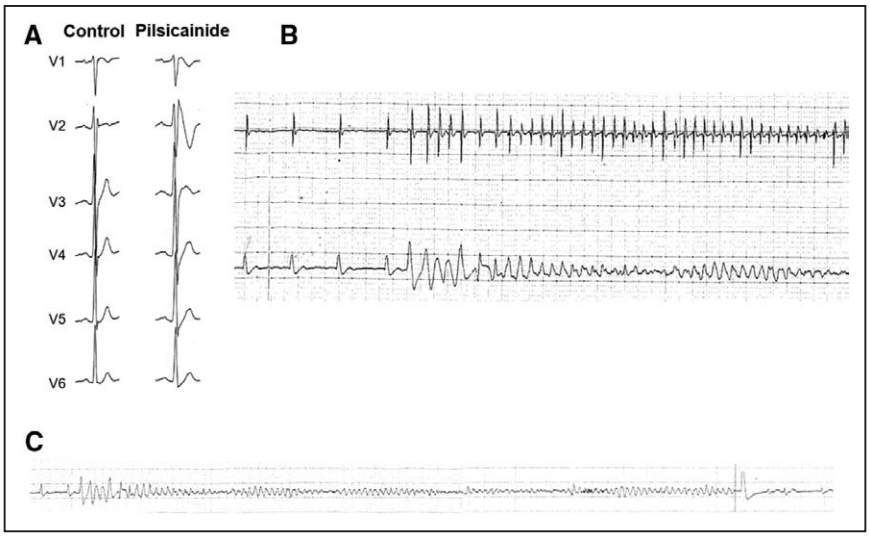

Figure 5. A case in the coronary artery spasm (CAS)–alone group with Brugada-like ECG pattern. **A**, Brugada type 1 ECG pattern emerged just after intravenous pilsicainide administration. **B**, Recurrent ventricular fibrillation (VF) induced by a single premature ventricular contraction despite an optimal treatment with calcium channel blockers (CCB). **C**, An appropriative implantable cardioverter-defibrillators (ICD) shock terminated ventricular fibrillation.

in OHCA survivors with CAS and that single induction test for CAS or VF alone is not enough to elucidate the underlying pathophysiology. Thus, the dual induction tests for CAS and VF may be considered for all OHCA survivors without organic heart disease.

CAS and VAs

The prevalence of CAS in patients who were resuscitated from cardiopulmonary arrest was reported as 7.4% in Japan[22] and 1.4% to 3.3% in the West.[4,23] Furthermore, it is also known that silent myocardial ischemia because of CAS could induce fatal arrhythmias.[4] These findings indicate that CAS is a common cause of OHCA, and provocation test for CAS is essential to properly diagnose it. However, no provocation test for CAS with intracoronary ACh or ergonovine was performed in the previous studies for OHCA survivors without organic heart disease.[16,24] In the present study, ACh provocation test was performed in all patients, including those with Brugada-like ECG pattern. The results showed that CAS was present in two thirds of OHCA survivors without organic heart disease. Then, another VF induction test was performed to examine the possible existence of primary electric instability. The result showed that the patients with CAS were divided into 2 groups: CAS-alone and both-positive groups. OHCA in the CAS-alone group was likely to be caused by ischemia derived from CAS, whereas that in the both-positive group might be caused by either lethal VAs or CAS. In the present study, CAS alone was the likely cause of OHCA in a minority of patients classified into the CAS-alone group. Furthermore, we found that the incidence of recurrent VF tended to be different between the CAS-alone and both-positive groups. Indeed, in the CAS-alone group, VF recurred in only one patient with Brugada syndrome, irrespective of exacerbation of CAS. Importantly, the patients in the both-positive group had higher incidence of recurrent VF, although the causative role of CAS for OHCA remains unclear. The difference in long-term prognosis among OHCA survivors with CAS by the presence or absence of primary electric disorder could account for the discrepancies in outcomes of OHCA survivors with CAS in the previous studies.[4,10,13,23,25] Altogether, we were unable to elucidate the exact mechanism, including the role of CAS, for the occurrence of VF in the patients of both-positive group by the dual induction test alone. Thus, after suppressing CAS completely by the treatment with CCBs, we may need to further explore the cause of electric instability among both-positive group patients by adding systematic drug provocation and advanced imaging to detect latent LQTS, catecholaminergic polymorphic VT, arrhythmogenic right ventricular cardiomyopathy, and subclinical myocarditis.

ICD Implantation for OHCA Survivors Without Organic Heart Disease

The secondary prevention trials of SCD have been robust, showing a consistent effect of improved survival with ICD therapy compared with antiarrhythmic drug therapy alone.[8] Primary electric abnormalities include Brugada syndrome, LQTS and short QT syndromes, catecholaminergic polymorphic VT, and idiopathic VF, all of which have a certain genetic background.[5,6] There is a consensus that patients with prior OHCA are at high risk for recurrent fatal arrhythmic events, for whom ICD therapy is recommended.[9] Additionally, patients with syncope of undetermined origin in whom clinically relevant VT/VF is induced at electrophysiological study should also be considered as candidates for ICD therapy.[9,26] Thus, in the present study, it was reasonable to implant an ICD in the patients who were classified to the VAs-alone and both-positive groups by the dual induction tests and those with Brugada syndrome. Indeed, 7 cases in the VAs or the Brugada syndrome group had a recurrence of VF, where ICD therapy succeeded in saving all the patients.

In contrast, the current guidelines are silent with respect to the use of an ICD as a secondary prevention for lethal VAs because of CAS.[9] Indeed, the indication of ICD for this population has been controversial because CAS is considered as a treatable cause of OHCA with CCBs and other medications.[4,11,13,23] We think that the present findings should offer a new viewpoint on this important issue. As elucidated by the dual induction tests in the present study, OHCA survivors with CAS are inhomogeneous in pathogenesis. Indeed, lethal VAs in the CAS-alone group are likely to result from pure ischemia

caused by CAS, whereas in the both-positive group, CAS and coexisting primary electric disorders may have synergistic or additive effects on the development of OHCA. Because it is difficult to predict or control the recurrence of VF in the latter group, ICD may also be indicated for the secondary prevention of VF. Actually, in the present study, 6 of 18 patients without Brugada syndrome in the both-positive group (33%) were saved by ICD shocks from recurrent VF of undetermined origin. In contrast, 5 OHCA survivors with CAS alone and without Brugada syndrome had no episode of recurrent VF under adequate medications, and they showed a better prognosis as compared with those with Brugada syndrome. These findings indicate that ICD may not be essential for OHCA survivors with CAS alone and without Brugada syndrome. For the management strategy without ICD implantation for OHCA survivors, optimal medical treatments, including CCBs and its compliance, are apparently important because discontinuing or decreasing medications in vasospastic angina patients significantly increases the risk of relapse of lethal arrhythmic events as we previously reported.[12]

Study Limitations

Several limitations should be mentioned for the present study. First, the present study was a single-center, exploratory study with a relatively small number of patients. However, we think that the prospective design of the present study protocol should provide important clinical implications of the dual induction tests. Second, the prevalence of CAS in OHCA survivors without organic heart diseases may vary by race. Indeed, a high prevalence of CAS has been reported in Japanese OHCA survivors,[27] whereas the prevalence may be lower in whites.[28] However, Ong et al have recently demonstrated that epicardial and microvascular spasm are frequently noted even in white patients with angina and unobstructed coronary arteries.[29] Thus, the present findings should be reconfirmed in an international, prospective, and large-scale study. Third, because the purpose of the present study was to evaluate the clinical usefulness of the dual induction tests but not to thoroughly elucidate the underlying cause of OHCA in all patients, we did not systemically perform imaging tests or drug challenge tests to detect other possible primary electric disorders (eg, LQTS, catecholaminergic polymorphic VT, arrhythmogenic right ventricular cardiomyopathy, and subclinical myocarditis). We also did not perform targeted genetic screening for the patients with positive VF induction test, including those with Brugada syndrome. Thus, we did not identify a definite diagnosis of the disease causing OHCA in the 26 patients (55%) classified into VAs-alone, both-positive, or both-negative groups. Fourth, the prevalence of Brugada syndrome in the present study might have been underestimated because Brugada-like ECG pattern changes over time.[30] Fifth, although 10 patients had early repolarization ECG pattern, of which the presence is indicated as a high risk for fatal VAs,[18] we were unable to elucidate its impact on the results of dual induction tests. Sixth, the small sample size of our subjects did not allow us to compare the long-term prognosis among groups classified by the dual induction test, with an appropriate correction for baseline differences. In future studies, the systematic and rigorous clinical tests, as well as genetic screenings for familiar SCD, should be performed to unmask latent primary electric diseases in the patients classified into VAs-alone, both-positive, or both-negative groups by dual induction tests. Although, however, the purpose of the present study was to evaluate the clinical usefulness of the dual induction tests but not to thoroughly elucidate the underlying cause of OHCA in all patients, we were able to detect underlying causes of OHCA in terms of coronary vasomotion and electrophysiological abnormalities in 94% of our patients by the dual induction tests. Thus, we think that the dual induction tests could substantially contribute to risk stratification for the recurrence of life-threatening arrhythmias in patients with unexplained cardiac arrest.

Conclusions

In conclusion, the present study indicates that among OHCA survivors, those with CAS alone and without Brugada syndrome in the dual induction tests may be at low risk for recurrent sudden death and subsequent ICD firing.

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Disclosures

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Usefulness of Testing for Coronary Artery Spasm and Programmed Ventricular Stimulation in Survivors of Out-of-Hospital Cardiac Arrest

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SUPPLEMENTAL MATERIAL

Supplemental Table: Baseline Patient Characteristics of the 4 Groups

	Overall (n=47)	CAS-alone (n=7)	VAs-alone (n=13)	Both-positive (n=24)	Both-negative (n=3)	P value
Age, year	43.3±13.9	49.9±16.9	35.9±11.1	45.2±13.3	44.3±15.2	0.097
Male, n (%)	44 (94)	7 (100)	12 (92)	22 (92)	3 (100)	0.846
BMI, kg/m^2	21.9±2.9	22.7±3.8	20.8±2.3	22.0±2.5	23.8±6.0	0.483
Coronary risk factors						
Hypertension, n (%)	8 (17)	1 (14)	2 (15)	5 (21)	0 (0)	0.820
Dyslipidemia, n (%)	15 (32)	4 (57)	1 (8)	8 (33)	2 (67)	0.064
Diabetes mellitus, n (%)	2 (4)	0 (0)	1 (8)	0 (0)	1 (33)	0.046
Current Smoking, n (%)	27 (57)	4 (57)	9 (69)	14 (58)	0 (0)	0.178
Familial history of SCD, n (%)	4 (9)	0 (0)	3 (23)	1 (4)	0 (0)	0.180
Symptoms before OHCA, n (%)	17 (36)	3 (43)	3 (23)	10 (42)	1 (33)	0.700
Chest pain, n (%)	13 (28)	3 (43)	1 (8)	8 (33)	0 (0)	0.280
Palpitation, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Syncope, n (%)	5 (11)	0 (0)	1 (8)	3 (13)	1 (33)	0.446
Pre-syncope, n (%)	2 (4)	0 (0)	1 (8)	1 (4)	0 (0)	0.844

Situation at OHCA						
Rest onset, n (%)	29 (62)	4 (57)	10 (77)	12 (50)	3 (100)	0.204
Effort onset, n (%)	18 (38)	3 (43)	3 (23)	12 (50)	0 (0)	0.204
ECG findings						
Brugada-like ECG pattern, n (%)	16 (34)	2 (29)	8 (62)	6 (25)	0 (0)	0.075
ER ECG pattern, n (%)	10 (21)	2 (29)	2 (15)	5 (21)	1 (33)	0.860
QTc, msec	406.7±28.7	404.3±28.9	405.5±33.7	412.0±25.6	375.3±16.9	0.136
AF, n (%)	9 (19)	1 (14)	2 (15)	5 (21)	1 (33)	0.883
Positive for LP, n (%)	25 (53)	2 (29)	8 (62)	13 (54)	2 (67)	0.841
Echocardiography						
LVEF, %	66.8±6.8	67.1±6.4	64.0±7.6	67.3±6.5	72.9±4.5	0.299
LVDd, mm	46.9±3.6	47.8±3.7	46.0±3.8	47.5±3.4	43.9±2.9	0.237
Laboratory data						
Sodium, mEq/L	140.8±2.7	139.1±3.2	140.9±2.0	141.2±2.8	141.0±3.6	0.594
Potassium, mEq/L	3.94±0.55	4.16±0.50	3.87±0.52	3.88±0.56	4.30±0.72	0.656
Chloride, mEq/L	103.5±2.8	103.0±3.7	104.0±2.6	103.4±2.9	103.7±2.5	0.788
Cr, mg/dl	0.88±0.24	0.69±0.16	0.95±0.29	0.89±0.22	0.93±0.15	0.115
Hb, g/dl	14.0±1.7	13.6±1.6	13.9±1.3	14.4±1.5	12.4±4.0	0.461
TC, mg/dl	179.9±31.2	189.4±37.4	170.9±17.0	178.4±34.8	208.3±19.9	0.270

LDL, mg/dl	113.7±30.0	127.7±45.3	104.5±13.6	110.4±29.2	147.3±22.7	0.120
HDL, mg/dl	43.8±14.1	35.9±6.7	47.4±16.0	45.4±14.4	34.3±5.5	0.169
TG, mg/dl	153.1±95.7	189.5±161.0	169.9±106.9	135.4±72.9	149.3±37.6	0.716
HbA1c, %	5.65±0.51	5.50±0.23	5.71±0.76	5.61±0.37	6.00±0.53	0.418
BNP, pg/ml, median (IQR)	13.2 (5.8-47.4)	23.0 (9.0-48.4)	7.6 (5.8-23.9)	17.2 (6.4-74.5)	20.4 (5.8-193.0)	0.521
hs-CRP, mg/dl, median (IQR)	0.11 (0.03-0.21)	0.11 (0.02-0.18)	0.10 (0.02-0.28)	0.11 (0.03-0.16)	0.23 (0.12-0.36)	0.615
Medications						
CCBs, n (%)	31 (66)	7 (100)	0 (0)	24 (100)	0 (0)	NA
Benidipine, n (%)	23 (49)	5 (71)	0 (0)	18 (75)	0 (0)	NA
Diltiazem, n (%)	7 (15)	1 (14)	0 (0)	6 (25)	0 (0)	NA
Anti-arrhythmic agents, n (%)	3 (6)	0 (0)	1 (8)	1 (4)	1 (33)	0.225

Results are expressed as mean±SD, median (IQR) or number (%).

AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; CCB, calcium channel blocker; Cr, creatinine; ECG, electrocardiogram; ER, early repolarization; Hb, hemoglobin; HDL, high density lipoprotein; hs-CRP, high sensitivity C-reactive protein; LDL, low density lipoprotein; LP, late potential; LVDd, left ventricular dimension diastolic; LVEF, left ventricular ejection fraction; QTc, corrected QT interval; SCD, sudden cardiac death; SD, standard deviation; TC, total cholesterol; TG, triglyceride; VF, ventricular fibrillation.