Spasm Provocation Tests under Medication may Help Decide on Medical or Mechanical Therapy in Patients with Aborted Sudden Cardiac Death due to Coronary Spasm

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Abstract:

Background  The decision to perform medical or mechanical therapy in patients with aborted sudden cardiac death (ASCD) due to coronary spasm is controversial. The Japanese Circulation Society guidelines for the diagnosis and treatment of patients with coronary spastic angina mentioned that implantable cardioverter-defibrillator (ICD) is one option in patients with ASCD due to coronary spasm.

Objectives  We investigated the usefulness of spasm provocation tests under medications in five patients with ASCD due to coronary spasm.

Methods  We performed the spasm provocation tests under medications in five ASCD patients due to coronary spasm. Pharmacological spasm provocation tests, including five acetylcholine (ACh) tests, two ergonovine (ER) tests, and two ACh added after ER tests, were performed to estimate the effect of medications to suppressing the next fatal spasms.

Results  ACh tests under medications did not provoke spasm in one patient but did provoke in two patients. In the remaining two patients, neither the ACh test nor the ER test provoked spasm, but the ACh added after ER test induced a focal spasm in one coronary artery. We increased the medication dosage in four patients. An ICD was implanted in two patients, including one with refractory spasm and one with left main trunk spasm. One patient died due to pulseless electrical activity without ventricular fibrillation, while the remaining four patients survived.

Conclusions  Spasm provocation tests under medication in patients with ASCD due to coronary spasm may be an option when deciding on medical or mechanical therapy.

Key words: ventricular fibrillation, coronary artery spasm, implantable cardioverter-defibrillator, aborted sudden cardiac death, medications

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Introduction

In 1986, intracoronary acetylcholine (ACh) testing was first reported by Yasue and Okumura (1). Since then, intracoronary ACh test has become popular as a spasm provocation test worldwide, as has the ergonovine (ER) test (2-6). We previously reported the usefulness of sequential spasm provocation tests in the clinic in 2000 (7). Single spasm provocation test, such as the ACh test or ER test alone, may fail to detect clinical everyday spasm in the cardiac catheterization laboratory. Sequential spasm provocation tests may therefore be extremely powerful spasm provocation tests (8).

According to the Japanese Circulation Society (JCS) guidelines for the diagnosis and treatment of patients with coronary spastic angina (CSA), cessation of vasodilators for more than 48 h before the spasm provocation tests is recommended (9).

We have experienced patients with aborted sudden cardiac death (ASCD) due to pure coronary artery spasm in the clinic. The JCS guidelines mentioned an implantable cardioverter-defibrillator (ICD) as a treatment option for...
these patients (9), and this device was inserted in some patients (10, 11), while aggressive medication without ICD implantation was performed in other patients. However, the decision to perform medical or mechanical therapy in patients with ASCD due to coronary spasm is controversial, and at present, cardiologists have no way to identify those patients who would most benefit from an ICD.

We herein report the results of spasm provocation tests under the medication in five ASCD patients due to coronary spasm.

### Methods

We recruited five patients with ASCD due to coronary spasm who had undergone spasm provocation tests under medications. All five patients were ventricular fibrillation (VF) survivors, as shown in Table 1. The spasm provocation data are shown in Table 2, and the total doses of precise vasodilators, including calcium channel blockers, are shown in Table 3. We have already reported three cases (case 2, 3, and 4) (12, 13).

The study protocol complied with the Declaration of Helsinki. Written informed consent was obtained from all patients before performing the pharmacological spasm provocation tests, and the protocol of this study was in agreement with the guidelines of the ethical committee at our institution.

### Statistical analyses

Data analyses were performed using the SPSS software program (version 22.0, IBM Japan, Ltd., Tokyo, Japan). All data were presented as the median (minimum, maximum) and were analyzed by Fisher’s exact test with correction or the Mann-Whitney test. p<0.05 was considered significant.

### Case Presentations

#### Case 1

A 68-year-old man was taken to our hospital via ambu-

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**Table 1. Clinical Findings in 5 Patients with Aborted Sudden Cardiac Death Due to Coronary Spasm.**

| No | Age | Sex | Diagnosis | Risk factor | Duration (month) | Organic stenosis | OMI | EF | ICD | Prognosis | Before medication |
|----|-----|-----|-----------|-------------|-----------------|-----------------|-----|----|-----|-----------|------------------|
| 1  | 68  | M   | VF        | C smoker    | 52              | no              | yes | 42%| no | alive    | Curvedilol 2.5 mg |
| 2  | 52  | M   | VF        | C smoker/HT | 11              | #7 (50%)        | no  | 78%| yes| alive    | Terumisartan 40 mg |
| 3  | 59  | M   | VF        | C smoker/HT/DL | 128            | no              | no  | 72%| no | alive    | Amlodipine 5 mg   |
| 4  | 73  | M   | VF        | NC smoker/DM/DL | 126            | no              | no  | 75%| no | alive    | Amlodipine 5 mg   |
| 5  | 61  | M   | VF        | C smoker    | 15              | no              | no  | 78%| yes| dead     | none              |

OMI: old myocardial infarction, EF: ejection fraction by ultrasonography, ICD: implantable cardioverter-defibrillator, M: male, VF: ventricular fibrillation, C: current, NC: non-current, HT: hypertension, DM: diabetes mellitus, DL: dyslipidemia

**Table 2. Spasm Provocation Tests under Medications in 5 Patients with Aborted Sudden Cardiac Death Due to Coronary Spasm.**

| No | Spontaneous spasm or ST change | Spasm provocation test without medication | Spasm provocation test under medications |
|----|---------------------------------|------------------------------------------|----------------------------------------|
| 1  | ST ele in ANT                   | ACh (L:50) #6 (total) #11 (diffuse)      | ACh (L:20/50/100/200) no spasm         |
|    |                                 | ACh (R:20) #3 (total)                     | ACh (R:20/50/80) no spasm              |
|    |                                 |                                          | ER (L:64) no spasm                      |
|    |                                 |                                          | ER (R:40) no spasm                      |
|    |                                 |                                          | ACh (L:200) after ER (64) no spasm      |
|    |                                 |                                          | ACh (80) after ER (40) #3(focal)        |
| 2  | (-)                             | ACh (L:20) #5 (focal) #7 (focal)         | ACh (L:20/50/100/200) no spasm         |
|    |                                 | ACh (R:20) #4 (diffuse) after nitroglycerine 0.1 mg in LCA | ACh (R:50/80) no spasm |
|    |                                 |                                          | ER (L:64) no spasm                      |
|    |                                 |                                          | ER (R:40) no spasm                      |
|    |                                 |                                          | ACh (200) after ER (64) #7(focal)       |
|    |                                 |                                          | ACh (R:80) after ER (40) no spasm       |
| 3  | ST ele in INF & ANT             | (-)                                      | ACh (L:50/100) no spasm                |
|    |                                 |                                          | ACh (R:50) no spasm                     |
| 4  | Negative T in ANT              | ACh(L:25) #7 (diffuse) #11 (diffuse)     | ACh (L:25/50/100) #8(focal) #13(diffuse) |
|    |                                 | ACh (R:25) #2 (total)                     | ACh (R:25) #2 (focal)                   |
| 5  | (-)                             | ACh (L:20) #6(diffuse) #11(diffuse)      | ACh (L:50/100) #6(diffuse) #11(diffuse) |
|    |                                 | ACh (R:20) #1 (subtotal)                 | ACh (20/50/80) #4 AV (total)            |

ACh: acetylcholine, ER: ergonovine, R: right coronary artery, L: left coronary artery
lance because of resistant VF. Self-sinus rhythm was ob-
tained by direct current after the administration of amiodar-
one hydrochloride anti-arrhythmic agents, as shown in
Fig. 1A, B. Cardiopulmonary support was continued for ap-
proximately 25 minutes. Although coronary arteriography
(CAG) was performed because of ST segment elevation in
the anterior leads (Fig. 1C, D), no fixed stenosis was found
(Fig. 2A, B). He completely recovered without any brain
damages with hypothermia therapy and respiratory intuba-
tion for three days. Anterior myocardial infarction due to
coronary spasm was complicated, and a reduced left ven-
tricular function was observed, as shown in Table 1. We per-
formed the spasm provocation tests to clarify the presence
of coronary artery spasm under no medication. Intracoronary
injection of ACh 20 μg into the left coronary artery (LCA)
documented total spasm at proximal left anterior descending
(LAD) artery and diffuse spasm at the left circumflex artery
(LCX), as shown in Fig. 2C, E. We administered nitrate (0.1
mg nitroglycerine) into the LCA to relieve refractory spasm
4 minutes later. Intracoronary injection of 50 μg ACh into
the right coronary artery (RCA) provoked total spasm at the
mid RCA, as shown in Fig. 2D, F. We diagnosed him as a

Table 3. Medications in 5 Patients with Aborted Sudden Cardiac Death Due to Coronary Spasm.

| No | Vasodilators on admission | Number of CCB | Vasodilators after the initial spasm provocation tests | Number of CCB | Vasodilators after the spasm provocation tests under medications | Number of CCB |
|----|---------------------------|---------------|-------------------------------------------------------|---------------|---------------------------------------------------------------|---------------|
| 1  | 0                         | 0             | 3 (Dil-R 200 mg/Beni 8 mg, ISMN 40 mg)                 | 2             | 4 (Dil-R 200 mg/Beni 8 mg, ISMN 40 mg/ Nito 15 mg) statin      | 2             |
| 2  | 0                         | 0             | 4 (Dil-R 200 mg/Nif-R 80 mg/ISMN 40 mg/Nito-tape 40 mg)| 2             | 4 (Dil-R 200 mg/Nif-R 80 mg/ISMN 40 mg/Nito-tape 40 mg) statin| 2             |
| 3  | 1 (Amlo 5 mg)             | 1             | 2 (Dil-R 100 mg/Amlo 5 mg)                             | 2             | 4 (Dil-R 200 mg/Beni 8 mg/ISMN 40 mg/ Nito-tape 40 mg) statin| 2             |
| 4  | 1 (Amlo 5 mg)             | 1             | 2 (Amlo 5 mg/ISMN 40 mg) statin                         | 1             | 5 (Dil-R 200 mg/Beni 8 mg/ISMN 40 mg/ Nito 15 mg/ Nito-tape 40 mg) statin | 2             |
| 5  | 0                         | 0             | 2 (Beni 8 mg/ISMN 40 mg) statin                         | 1             | 4 (Beni 8 mg/Dil-R 200 mg/ISMN 40 mg/ Nito 15 mg) statin      | 2             |

Mean no 0.4 (0-1) 0.4 (0-1) 2.6 (2-4) * 1.6 (1-2) * 4.2 (4-5) **# 2.0 (2) *

R: right coronary artery, L: left coronary artery, Amlo: amlo-adi, Dil-R: dil-tizem R, Beni: benidipine, Nif-R: nifedipine R, ISMN: isosorbide mononitrate, Nito: nicorandil, Nito-tape: nitrile tape, CCB: calcium channel blocker, *: p<0.01 & **: p<0.001 vs. before admission, #: p<0.05 vs. initial spasm provocation test, bold type: additional medicine

Figure 1. ECG findings. A: ventricular fibrillation on admission. B: after successful defibrillation. C: 12-lead ECG after successful defibrillation. D: 12-lead ECG before emergency CAG. E: 12-lead ECG after 2 days’ admission. Ventricular fibrillation was observed on admission (A), and ST-segment elevation in the anterior leads was found after successful defibrillation. (C/D) A negative T wave in the anterior leads was recognized on the day after admission (E).
VF survivor due to severe coronary spasm. After the administration of multiple vasodilators, including two calcium channel blockers (benidipine hydrochloride 8 mg/day and diltiazem R 200 mg/day twice a day) and isosorbide mononitrate 40 mg/day twice a day, we performed the sequential spasm provocation tests 3 months later to investigate whether or not the medications suppressed the coronary artery spasm. No provoked spasms were noted on single spasm provocation tests, such as the ACh test and just ER tests alone, as shown in Fig. 3A to F. Adding ACh 200 μg after intracoronary ER 64 μg into the LCA also provoked no spasm (Fig. 3G), although adding intracoronary 80 μg ACh after ER 40 μg into the RCA induced diffuse spasm at the mid RCA (Fig. 3H). Nicorandil 15 mg was added to the above medications. The patient refused ICD implantation. He has maintained good control under medications with multiple vasodilators as an outpatient without ICD for 52 months.

Case 2

A 52-year-old man recovered from VF suffered while jogging leisurely with an automated external defibrillator and cardiac massage by a bystander. He was transferred to our hospital via ambulance. Under intubation with hypothermia therapy, he completely recovered without any irreversible complications. He had had neither chest symptom nor a history of syncope during his daily life for 52 years. We performed CAG without premedication on day 10 of admission. His LCA showed moderate stenosis at the left main trunk (LMT) and mid LAD artery. The intracoronary administration of 20 μg ACh into the LCA induced a focal spasm at the LMT and mid LAD artery without any chest symptoms or ischemic electrocardiographic changes. After the spontaneous relief of spasm, we administered 20 μg ACh into the RCA. Diffuse distal spasm was documented without any chest symptoms or ischemic electrocardiographic changes. After the administration of nitrate, moderate stenosis (50%) was found at segment 7. We diagnosed him as a VF survivor due to silent severe multiple coronary spasm including LMT. We administered abundant vasodilators, including 2 calcium channel antagonists (nifedipine CR 80 mg/day and diltiazem R 200 mg/day) and nitrates (isosorbide mononitrate 40 mg/day and nitrate tape 40 mg/day) instead of telmisartan. We decided to implant a subcutaneous-ICD (S-ICD) in this patient because he had silent severe coronary spasm including LMT. After the implantation of S-ICD, we per-
formed the pharmacological spasm provocation tests under the above medications to check whether or not these medications suppressed the LMT spasm. The intracoronary administration of ACh 20/50/100/200 μg into the LCA or 80 μg into the RCA did not induce spasm. Furthermore, the intracoronary injection of ergonovine (ER) 64 μg into the LCA or 40 μg into the RCA did not result in any coronary vasoconstriction. Adding ACh 200 μg after ER 64 μg into the LCA did not induce any spasm. We did not perform percutaneous coronary intervention at segment 7 because of the 50% stenosis. We believed that this aggressive medication would suppress the next fatal ventricular arrhythmia due to coronary spasm in the future. He was discharged in a good condition on day 28. He had no chest symptoms, syncopal attack or appropriate ICD shocks for 11 months.

Case 3

A 59-year-old man was admitted to our hospital via ambulance due to severe chest pain without ischemic electrocardiogram (ECG) changes. Emergency CAG was performed, and the patient’s RCA showed severe spasms. Following the administration of abundant nitrates into the responsible vessels, both coronary arteries gradually dilated, and no fixed stenosis was recognized. He was diagnosed with CSA and discharged after receiving two calcium-channel blockers (diltiazem R: 100 mg/day before sleep & amlodipine: 5 mg/day in the morning). Six months later, he was readmitted to our hospital via ambulance due to severe chest pain. His ECG demonstrated ST elevation in the inferior leads. After several administrations of nitroglycerine, the ST elevation gradually decreased. However, VF occurred, and the patient recovered to a sinus rhythm by the application of direct current. Emergency CAG was performed, and normal coronary angiograms were found. Prior to discharge, a spasm provocation test of ACh was performed under medical therapy including three vasodilators (diltiazem R: 200 mg/day, bendipidine: 8 mg/day & isosorbide mononitrate: 40 mg/day). Intracoronary injection of 100 μg ACh into the LCA or 50 μg ACh into the RCA provoked no spasm under the medical therapy, and we believed that this therapy would be effective in suppressing the patient’s chest pain attacks. For 128 months after the spasm provocation test under medications, this patient has been well except one urgent admission without a hospital stay.

Case 4

A 72-year-old man was transferred to our hospital via ambulance as a VF survivor. On emergency CAG, no fixed stenosis was detected, despite the presence of negative T
changes in anterior leads. Following the administration of a calcium channel blocker (amlodipine: 5 mg/day) and nitrate (isosorbide mononitrate: 40 mg/day), he complained of no further chest pain. Prior to discharge under no medication, the intracoronary administration of 20 μg of ACh provoked 3-vessel spasms consisting of proximal RCA total spasms, mid-LAD diffuse spasms, and proximal-LCX diffuse spasms. Approximately four months later, he was readmitted to our hospital via ambulance due to recurrent chest pain attacks. We administered another vasodilator including diltiazem R 200 mg/day and nicorandil 15 mg/day. Under full medication, a spasm provocation test was performed. In the RCA, intracoronary injection of 20 μg ACh provoked total spasm at proximal RCA. Meanwhile, in the LCA, the injection of 100 μg of ACh provoked diffuse spasms in both the distal LAD and proximal LCX artery. We judged that this medication would not be sufficient to suppress the next attack and switched from amlodipine (5 mg) to benidipine 8 mg/day and increased the dose of the nitrates (nitrate tape: 40 mg/day). The stimulated electrophysiological study was negative. The patient did not agree to implantation of an ICD device. After receiving these medications, his chest symptoms gradually improved and ultimately disappeared. Furthermore, under the above medications, including a statin, the patient complained of no chest pain for 126 months, without urgent admissions to the hospital.

Case 5

A 61-year-old man was transferred to the hospital because of severe chest oppression. He had a history of syncope of unknown cause two years ago and was a current smoker. Because VF had been observed in the ambulance, two cycle shocks by an automated external defibrillator recovered his VF. No ischemic ECG changes were found on admission. CAG was performed one week later, and no fixed stenosis was found. An ACh spasm provocation test was performed under no medication. An intracoronary injection of ACh 20 μg into the RCA provoked subtotal spasm at the proximal RCA, while proximal-LAD and LCX diffuse spasms were documented by the intracoronary injection of ACh 20 μg into the LCA. Triple-vessel spasm was provoked by low-dose ACh administration accompanied by chest oppression and ischemic ECG changes. After the administration of medications including benidipine 8 mg and isosorbide mononitrate 40 mg/day for 7 days, triple-vessel spasm was also provoked by the single ACh test with chest oppression and ischemic ECG changes. Under sufficient medication, including benidipine 8 mg, diltiazem R 200 mg, isosorbide mononitrate 40 mg, nicorandil 20 mg and a statin, we reinvestigated the coronary response by the ACh test after 1 week. The intracoronary injection of ACh 50 μg into the RCA disclosed distal RCA subtotal spasm, while both LAD and LCX proximal diffuse spasm was documented by the administration of ACh 50 μg into the LCA. Ischemic ECG changes and chest oppression also recognized in both coronary arteries. We decided to implant an ICD because of refractory coronary spasm. Despite taking abundant medications, he was again transferred to another hospital due to syncope. At 15 months after ICD implantation, he died of pulseless electrical activity (PEA). His ICD showed no shocks and neither ventricular fibrillation nor tachycardia was recognized in the ambulance or at hospital admission.

Results

Under no medication, triple-vessel spasm was observed in four patients, and the remaining patient had multiple spasms, as shown in Table 2. We performed spasm provocation tests under medication to evaluate the effectiveness of medical therapy in five patients who had survived VF due to pure coronary spasm. Single ACh spasm provocation tests were performed in three patients, and sequential spasm provocation tests were underwent in two patients. ACh tests alone provoked typical spasm in two patients and did not provoke spasm in three patients. While ER tests alone provoked no spasm in two patients, the ACh added after ER test provoked single-vessel spasm in these patients. After the spasm provocation tests under medication, we strengthened medications to suppress coronary spasm. The mean number of vasodilators after the spasm provocation tests under medication were significantly higher than that in the initial diagnostic tests, as shown in Table 3. An ICD was implanted in two patients, including one with refractory spasm (case no. 5) and one with silent LMT spasm (case no. 2). One patient with ASCD due to refractory spasm died due to PEA but not VF.

Discussion

In this article, we described the results of spasm provocation tests under sufficient medication in five ASCD patients due to pure coronary spasm. We were able to strengthen the medications to suppress the next fatal events. However, one ASCD patient died due to PEA, but not VF. If we perform sequential spasm provocation tests to identify patients who require an ICD to suppress the next fatal ventricular arrhythmia due to coronary spasm, we may be able to detect these high-risky patients earlier in the future. Because spasm provocation tests under medication may be useful for identifying patients who need an ICD to suppress the next fatal arrhythmic events, we may be able to use these tests to decide whether or not to implant an ICD in ASCD patients due to pure coronary spasm.

Spasm provocation test under the sufficient medications

Spasm provocation tests were used to diagnose the presence of coronary artery spasm in the cardiac catheterization laboratory. According to the JCS guidelines, cessation of vasodilators for more than 48 h before pharmacological spasm provocation tests is needed for a strict diagnosis; however, we used this diagnostic method to clarify the ac-
tual vasospasticity under abundant medications in the clinic. In addition, we used sequential spasm provocation tests as the most powerful spasm provocation test to ensure an excellent future outcome in ASCD patients due to coronary spasm. However, cardiologists normally do not use these tests to determine the effectiveness of medical therapy for suppressing the onset of the next fatal ventricular arrhythmias or for deciding on the need to implant an ICD. Medical therapy is the first-line therapy for patients with ASCD due to coronary spasm. Eschalier et al. recommended the ER tests be performed before the implantation of an ICD in patients with ASCD due to possible coronary spasm (14, 15). When ER tests were negative under optimum medical therapies, they recommended individual discussion for ICD implantation; if the ER tests were positive, they recommended ICD implantation in all cases, even if the optimum treatment was already being administered. If ASCD patients due to coronary spasm had spasm provoked by the sequential spasm provocation tests, cardiologists were advised to implant an ICD positively. However, when ASCD patients due to coronary artery spasm had no spasm provoked by the sequential spasm provocation tests, physicians were advised to medicate these patients without ICD.

**Strategy for patients with ASCD due to coronary artery spasm without Brugada syndrome or early repolarization syndrome**

We should also perform the electrophysiological or arrhythmic study in ASCD patients with pure coronary spasm. If the electrophysiological or arrhythmic study is positive, we should implant an ICD in these patients, as shown in Fig. 4. Some CSA cases are complicated with early repolarization or Brugada syndrome (16). These patients’ prognosis are unfavorable compared to those of patients with pure CSA (17-19). We reported the findings of sequential spasm provocation tests in patients with refractory CSA under abundant medical therapies (13). If a provoked positive spasm is not noted on a sequential spasm provocation test under the optimal medical therapy in patients with ASCD due to coronary spasm, cardiologists and patients are free to select a course of medical treatment without ICD implantation, as shown in Fig. 4. However, if a single spasm provocation test, such as an ACh or ER test alone, shows a positive result under sufficient medical therapies, it may be better to implant an ICD. The indications of ICD insertion in patients with ASCD due to pure coronary artery spasm have not been established. As one option, we showed a schematic drawing of the strategy for ICD implantation in patients with ASCD due to pure coronary spasm using the sequential spasm provocation tests according to the medical therapy protocol shown in Fig. 5. If we performed the prospective sequential spasm provocation tests under sufficient medications in patients with ASCD due to coronary spasm in the future, we may be able to detect these patients who require an ICD to suppress the next fatal ventricular arrhythmia due to coronary spasm. Further studies will be necessary in order to investigate the implantation of ICD in patients with ASCD due to pure coronary spasm and further follow-up studies with the index regarding ASCD patients due to coronary spasm are needed as well.
Conclusions

By performing spasm provocation tests under sufficient medications in ASCD patient due to pure coronary spasm, we were able to strengthen the medical therapies. While one patient died of PEA (not VF), spasm provocation tests under medications remain a suitable option for deciding on medical or mechanical therapy in patients with ASCD due to pure coronary spasm.

Limitations

Several limitations associated with the present study warrant mention. We were only able to perform the spasm provocation tests under medications in just five of survivors VF due to pure coronary spasm. Furthermore, we were only able to perform sequential spasm provocation tests under medication in just two patients. Although we strengthened the medications after the spasm provocation tests, we lost one ASCD patient who had had an ICD implanted because of PEA.

The authors state that they have no Conflict of Interest (COI).

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