Abstract:
Objective  Life-threatening ventricular arrhythmias are recognized in patients with coronary spastic angina. Implantable cardioverter-defibrillators (ICDs) are effective in patients with structural heart disease and ventricular fibrillation. However, the optimal medication for patients with aborted sudden cardiac death (SCD) due to coronary artery spasm after the implantation of ICD remains controversial.

Methods  We investigated the medications and the numbers of appropriate ICD shocks in 137 patients with a history of aborted SCD due to coronary spasm.

Results  Appropriate ICD shocks were observed in 24.1% (33/137) of patients with aborted SCD due to coronary spasm during 41 months of follow-up. Only 15 (15.6%) of the 96 patients with ICDs received aggressive medical therapy, including two or three calcium-channel antagonists. The rate of appropriate ICD shocks was significantly higher in Western countries than in Asian countries (42.9% vs. 19.3%, p<0.01), whereas the medications did not differ between the two regions. Appropriate ICD shocks successfully resuscitated 33 patients. Three patients died due to second serious fatal arrhythmias.

Conclusion  Appropriate ICD shocks were recognized in a quarter of patients with aborted SCD due to coronary spasm and ICD implantation was effective for suppressing the next serious fatal arrhythmia in these patients. We should reconsider prescribing more medications after ICD implantation in patients with aborted SCD due to coronary artery spasm.

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

Introduction
Life-threatening ventricular arrhythmias after resuscitation from aborted sudden cardiac death (SCD) in patients with coronary artery spasm are a major problem in the clinical setting (1). Under optimal medical therapy, including calcium-channel antagonists or nitrates, in the majority of cases, coronary spastic angina shows a good clinical course, whereas patients with aborted SCD due to coronary artery spasm may have a poor prognosis (2-6). Implantable cardioverter-defibrillators (ICDs) have been effective in patients with structural heart disease and ventricular fibrillation (7). The majority of the clinical reports published in the recent era concluded that ICDs were useful in patients with aborted SCD due to coronary artery spasm (8-11). However, although these patients received optimal medical therapy, we had no data about the appropriate ICD shocks that were administered to patients with aborted SCD due to coronary spasm after ICD implantation. We analyzed the past reports about appropriate ICD shocks and the medications that were administered after ICD implantation in patients with aborted SCD due to coronary artery spasm. We also compared the rates of appropriate ICD shocks and medications in patients from Western and Asian countries.
**Materials and Methods**

**Study subjects**
We extracted the papers published about ICD implantation in patients with coronary spastic angina from the PubMed database. We were able to analyze 137 patients who underwent the implantation of an ICD after the aborted SCD due to coronary artery spasm. Among the 137 patients, one patient had coronary artery spasm and Burgada syndrome, another patient had cocaine-induced spasm and one underwent ICD implantation after the implantation of a sirolimus-eluting stent (Cypher). We investigated the frequency of appropriate ICD shocks and compared the coronary risk factors, arteries with proven spasm, the medications and the prognosis after the implantation of ICD between patients with and without appropriate ICD shocks. Moreover, we compared Western and Asian patients with aborted SCD due to coronary artery spasm after ICD implantation, because coronary artery spasm has been reported to occur more frequently in Asian countries than in Western countries.

**Statistical analysis**
All of the data were presented as the mean±1 standard deviation (SD). All of the categorical variables were analyzed by Fisher’s exact test with correction or by the Mann-Whitney U test. p values of <0.05 were considered to indicate statistical significance.

**Results**

### Appropriate ICD shocks
As shown in Table 1, 137 patients underwent ICD implantation after aborted SCD due to coronary artery spasm (8-38). During the follow-up period (41±28 months), appropriate ICD shocks were observed in 33 patients

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**Table 1. Appropriate Implantable Cardioverter-defibrillator Shocks in Patients with Aborted Sudden Cardiac Death Due to Coronary Artery Spasm.**

| Reference | Patient number of ICD implantation | Follow-up duration | Patient number with appropriate ICD shocks |
|-----------|-----------------------------------|--------------------|------------------------------------------|
| 12        | 2                                 | 4 m/11 m           | 2 (100%)                                 |
| 13        | 1                                 | 2 m                | 0                                         |
| 14        | 1                                 | -                  | 1 (100%)                                 |
| 11        | 7                                 | 3.5±3.2 year       | 4 (57.1%)                                 |
| 15        | 1                                 | 6 m                | 0*                                        |
| 16        | 1                                 | 18 m               | 0                                         |
| 17        | 1                                 | 4 m                | 1 (100%)                                 |
| 18        | 1                                 | 1 day              | 1 (100%)                                 |
| 19        | 1                                 | 14 m               | 0                                         |
| 20        | 1                                 | 18 m               | 0                                         |
| 10        | 1                                 | 6 m                | 0                                         |
| 21        | 1                                 | 2 m                | 0                                         |
| 22        | 1                                 | 24 m               | 0                                         |
| 23        | 1                                 | 3 m                | 1 (100%)                                 |
| 24        | 12                                | 19 m (1-48 m)      | 1** (8.3%)                               |
| 25        | 1                                 | 12 m               | 1 *** (100%)                              |
| 26        | 14                                | 32 m (17-46 m)     | 2 (14.3%)                                |
| 8         | 23                                | 2.9 years (median 2.1 year) | 4 (17.4%) |
| 27        | 13                                | 17±14 m (1-40 m)   | 1 (7.7%)                                 |
| 28        | 14                                | 69±82 m            | 5 (35.7%)                                |
| 29        | 1                                 | 24 m               | 1 (100%)                                 |
| 30        | 2                                 | 12 m               | 0                                         |
| 31        | 1                                 | 12 m               | 0                                         |
| 32, 33    | 2                                 | 36 m               | 1 (50%)                                  |
| 34        | 1                                 | -                  | 0*                                        |
| 35        | 6                                 | 18±23 m (6-60 m)   | 0                                         |
| 36        | 1                                 | 24 m               | 0*                                        |
| 37        | 1                                 | -                  | 1 **** (100%)                             |
| 38        | 24                                | 7.5 years (4.0-11.8 years) | 6 (25%) |
| **Total** | 137                               | **41±28 m**        | **33 (24.1%)**                             |

*: after percutaneous coronary intervention, **: with Burgada syndrome, ***: cocaine induced, ****: after SES (Cypher)

ICD: implantable cardioverter-defibrillator, m: month
in 55 (40.1%) patients, including 4 Western and 51 Asian patients. Invasive spasm provocation tests were performed significantly more frequently in Asian countries than in Western countries [46.8% (51/109) vs. 14.3% (4/28), p<0.01], while spasm provocation tests in both the RCA and LCA were performed significantly more frequently in Asian countries than in Western countries [22.0% (24/109) vs. 3.6% (1/28), p<0.05]. However, angiographic spontaneous spasm observed significantly more frequently in Western countries than in Asian countries [35.7% (10/28) vs. 0.9% (1/109), p<0.001].

**Coronary risk factors**

As shown in Table 2, we could only analyze the coronary risk factors in 43 (31.4%) patients; the records of the remaining 94 patients were missing data about coronary risk factors. Appropriate ICD shocks were observed in 7 (16.3%) of 43 patients, while the remaining 36 patients (83.7%) received no ICD shocks. The rates of male sex and a history of smoking in patients without appropriate ICD shocks were significantly higher than in those with appropriate ICD shocks.

**Proviable artery spasm**

We could only analyze the 63 (45.6%) cases involving provable artery spasm. These included 24 Western patients and 39 Asian patients. Appropriate ICD shocks were observed in 19 patients, while 44 patients had no appropriate ICD shocks. The incidence of provable spasm in each of the three coronary arteries did not differ between the patients with and without appropriate ICD shocks [right coronary artery (RCA): 68.4% (11/19) vs. 50.0% (22/44), ns, left circumflex artery (LCX): 57.9% (11/19) vs. 50.0% (22/44), ns, left anterior descending artery (LAD): 63.2% (12/19) vs. 72.7% (32/44), ns]. Moreover, the rates of provable spasm in each of the three coronary arteries of patients with appropriate ICD shocks did not differ between Western and Asian patients [RCA: 81.8% (9/11) vs. 50.0% (4/8), ns, LCX: 45.5% (5/11) vs. 75.0% (6/8), ns, LAD: 54.5% (6/11) vs. 75.0% (6/8), ns].

**Pharmacological spasm provocation tests**

Pharmacological spasm provocation tests were performed in 55 (40.1%) patients, including 4 Western and 51 Asian patients. The rate of appropriate ICD shocks was significantly

| Table 2. Comparisons of coronary risk factors between patients with and without appropriate ICD shocks. |
|---------------------------------------------------------------|
| With appropriate ICD shocks | Without appropriate ICD shocks | p value |
|-----------------------------|---------------------------------|---------|
| Number of patients          | 7                               | 36      |
| Age (y)                     | 46.7±10.1                       | 50.3±13.3| 0.075  |
| Male                        | 3 (42.9%)                       | 32 (88.9%)| 0.019  |
| History of smoking          | 3 (42.9%)                       | 31 (86.1%)| 0.038  |
| Hypertension                | 3 (42.9%)                       | 11 (30.6%)| 0.845  |
| Dyslipidemia                | 1 (14.3%)                       | 10 (27.8%)| 0.783  |
| Diabetes mellitus           | 0                               | 1 (2.8%) | 0.355  |

ICD: implatable-cardioverter debrillator
higher among patients from Western countries than those from Asian countries (42.9% vs. 19.3%, p<0.01), as shown in Fig. 1. However, the medications that were administered after the implantation of an ICD in patients with aborted SCD due to coronary spasm did not differ between patients from Western and Asian countries.

**The medications administered to patients with and without appropriate ICD shocks**

As shown in Table 5, the medications in patients with appropriate ICD shocks did not differ from those in patients without appropriate ICD shocks. One calcium-channel antagonist was administered to 77.3% of the patients with appropriate ICD shocks, whereas 83.8% of the patients without appropriate ICD shocks were treated with 1 calcium-channel antagonist. In contrast, more than 3 vasodilators were administered to 22.7% of the patients with appropriate ICD shocks, while 24.3% of the patients without appropriate ICD shocks were treated with three or four vasodilators. We could only analyze the dosage of calcium-channel antagonists and nitrates/nicorandilis in 45 (32.8%) patients (Table 6). Diltiazem and nicorandil were often administered to patients in Asian countries, while verapamil was most frequently administered in Western countries. However, with the exception of diltiazem, the dosages did not differ between the two countries. Eight patients were treated with amiodarone, including one patient with appropriate ICD shock.

**The prognosis after the appropriate ICD shocks**

Appropriate ICD shocks were effective in suppressing ventricular tachycardia in 3 patients, ventricular fibrillation or fibrillation in 9 patients and ventricular fibrillation in 21 patients. Three patients with aborted SCD due to coronary spasm, who had undergone the implantation of an ICD, died during the follow-up period. One patient died due to pulseless electrical activity despite the continuous delivery of electrical therapy by the ICD, the second patient died due to intractable ventricular fibrillation, and the third patient died due to electromechanical dissociation and severely reduced left ventricular contraction despite appropriate ICD therapy. With the exception of the 3 patients who died, all 33 who received appropriate ICD shocks were rescued from second ventricular fibrillation/tachycardia. As shown in Fig. 2, 8 patients each from Western and Asian countries received appropriate ICD shocks. Within 12 months, appropriate ICD shocks were recognized in 10 (62.5%) of 16 patients. The details of the periods in which the appropriate ICD shocks were delivered were not found in 17 patients.

**Discussion**

During the 41-month follow-up period, appropriate ICD shocks were recognized in 24.1% of the patients with...
Table 4. Medications and Spasm Sites in Aborted Coronary Spastic Angina Patients without Appropriate Implantable Cardioverter-defibrillator Shocks.

| Reference | Age/Sex | No of pts | Spasm vessel | Follow-up duration | Medication |
|-----------|---------|-----------|--------------|--------------------|------------|
| Western countries |         |           |              |                    |            |
| 13 | 70/M | 1 | LAD/LCX | 2 m | Verapamil 180 mg, ISMN 60 mg |
| 11 | 40/M | 1 | LAD | 60 m | Nifedipine 30 mg, Diltiazem 60 mg, Verapamil 120 mg, ISDN 20 mg |
| 53/M | 1 | LAD | 3 m | Verapamil 240 mg, ISDN 50 mg |
| 68/M | 1 | LAD | 27 m | Diltiazem 60 mg, Amlodipine 10 mg, ISDN 40 mg |
| 15 | 47/F | 1 | LAD | 6 m | Verapamil 320 mg, Transdermal Nitrate 15 mg |
| 16 | 60/M | 1 | RCA | 18 m | Diltiazem dose unknown, Nitrates dose unknown |
| 19 | 49/M | 1 | LAD/LCX | 14 m | Amlodipine 10 mg, Transdermal Nitrate 5 mg |
| 20 | 50/M | 1 | LAD/RCA | 18 m | CCB unknown |
| 10 | 58/F | 1 | RCA | 6 m | Nifedipine dose unknown |
| 21 | Middle age/F | 1 | LCX | 2 m | CCB unknown, Nitrates unknown |
| 22 | 46/M | 1 | unknown | 24 m | Diltiazem dose unknown, ISMN dose unknown |
| 30 | 2 | LAD & LCX | 12 m | Amlodipine & metropolol (1), CCB & nitrate (1) |
| 32, 33 | 54/M | 1 | LMT | 18 m | Nifedipine 30 mg, Verapamil 240 mg |
| 34 | 54/M | 1 | LAD | - | CCB unknown. Long-acting nitrate unknown |
| 36 | 59/M | 1 | RCA | 24 m | Nifedipine 60 mg, ISMN 60 mg |
| Asian countries |         |           |              |                    |            |
| 24 | 11 | unknown | 18.5±12.5 m | Benidipine 2/4/8 mg (1/2/2), Benidipine 8 mg/Diltiazem 200 mg (2), Diltiazem 200 mg (1), Amlodipine 5 mg (1), CCB (-) (2) |
| 26 | 12 | unknown | unknown | unknown | unknown |
| 27 | 12 | LAD(11)/LCX(12)/RCA(18) | 2.9 year (median 2.1 year) | Diltiazem (19), ISMN (13), Nicorandil (10) |
| 28 | 9 | unknown | 69±82 m | CCBs (9), nitrates or nicorandil (6) |
| 31 | 68/M | 1 | RCA | 12 m | Diltiazem 400 mg, ISDN 40 mg, Nicorandil 15 mg |
| 35 | 6 | unknown | 18±23 m | Nifedipine CR 40/60 mg & ISDN 40 mg (2/1), Nifedipine 40 mg & Nicorandil 15 mg (1), Amlodipine 5 mg & ISDN 40 mg (1), Diltiazem R 200 mg ISDN 40 mg Nicorandil 15 mg (1) |
| 38 | 18 | unknown | unknown | unknown | unknown |

M: male; F: female; No of pts: Number of patients; LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, LMT: left main trunk, m: month, ISDN: isosorbide dinitrate, ISMN: isosorbide mononitrate, CCB: calcium channel blocker, f: number of patient

aborted SCD due to coronary artery spasm who underwent ICD implantation. Only 15.6% (15/96) of the patients were treated with aggressive medical therapy including two or three calcium-channel antagonists. The rate of appropriate ICD shocks was significantly higher in patients from Western countries than in those from Asian countries; however, the medications did not differ between the two regions. Appropriate ICD shocks resuscitated 33 patients; 3 patients died due to second ventricular fibrillations/tachycardia. The implantation of ICDs in patients with aborted SCD due to coronary spasm was effective in resuscitating these patients from their next life-threatening ventricular arrhythmias. Although these 33 patients underwent ICD implantation, medications might not have been sufficient for suppressing the patients’ next life-threatening ventricular arrhythmias due to coronary artery spasm. We should administer more
calcium-channel antagonists and nitrates/nicorandil in these near-miss patients. We did not find any patients who were treated with aggressive medical therapy among the patients without ICD shocks. Three patients died despite receiving appropriate ICD shocks after aborted SCD. If they had received more aggressive medical therapy, such as two or three calcium-channel antagonists, the implantation of an ICD might have rescued them. The optimal medications in patients with aborted SCD due to coronary spasm remain controversial; however, cardiologists should reconsider administering multiple medications to patients who are at high risk of serious fatal arrhythmias due to coronary spasm.

Pharmacological spasm provocation tests were defined as class I according to the Japanese Circulation Society guidelines (39), while the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines defined the tests as class IIa or IIb (40, 41). With the exception of cardiologists who worked in small special institutions, Western cardiologists did not perform the pharmacological spasm provocation tests in cardiac catheterization laboratories. In contrast, Asian cardiologists have been performing these tests for more than 30 years. In this series, Asian cardiologists performed pharmacological spasm provocation tests more frequently than their Western counterparts.

**Table 5.** Comparisons of Medications in Patients with Aborted Sudden Cardiac Death with and without Appropriate Implantable Cardioverter-defibrillator Shocks.

| Medication known | With appropriate ICD shocks | Without appropriate ICD shocks | p value | a vs. b |
|-----------------|-----------------------------|--------------------------------|---------|--------|
|                 | Total [a] | Western | Asian | p value | Total [b] | Western | Asian | p value | [a] vs. [b] |
| Medication unknown | 11 | 2 | 9 | 0.906 | 2 (3.4%) | 0 | 2 (3.4%) | 0.944 | 0.350 |
| 1 Ca | 17 (77.3%) | 6 (60.0%) | 11 (91.7%) | 0.078 | 62 (83.8%) | 13 (81.2%) | 49 (64.5%) | 0.780 | 0.482 |
| 2 Ca | 4 (18.1%) | 3 (30.0%) | 1 (8.3%) | 0.078 | 10 (13.5%) | 3 (18.8%) | 7 (12.1%) | 0.780 | 0.612 |
| 3 Ca | 1 (4.5%) | 1 (10.0%) | 0 | 0.078 | 0 | 0 | 0 | 0.517 | 0.517 |
| Nitrate or nicorandil | 13 (59.1%) | 5 (50%) | 8 (66.7%) | 0.078 | 55 (74.3%) | 12 (75.0%) | 43 (64.1%) | 0.944 | 0.167 |
| No medication | 0 | 0 | 0 | 0.078 | 2 (2.7%) | 0 | 2 (3.4%) | 0.906 | 0.209 |
| 1 vasodilator | 7 (31.8%) | 4 (40.0%) | 3 (25.0%) | 0.078 | 12 (16.2%) | 2 (12.5%) | 10 (17.2%) | 0.942 | 0.167 |
| 2 vasodilators | 10 (45.6%) | 6 (20.0%) | 8 (66.7%) | 0.078 | 42 (56.8%) | 12 (75.0%) | 30 (51.7%) | 0.167 | 0.209 |
| 3 vasodilators | 5 (22.7%) | 4 (40.0%) | 1 (8.3%) | 0.078 | 14 (18.9%) | 1 (6.3%) | 13 (24.4%) | 0.270 | 0.693 |
| 4 vasodilators | 0 | 0 | 0 | 0.078 | 4 (5.4%) | 1 (6.3%) | 3 (5.3%) | 0.865 | 0.612 |
| Total | 33 | 12 | 21 | 0.078 | 104 | 16 | 88 | 1.000 | 0.106 |

Ca: calcium channel antagonist, ICD: implantable cardioverter-defibrillator

**Table 6.** Comparisons of Dose of Calcium-channel Antagonists and Nitrates/nicorandil in Patients with Aborted Sudden Cardiac Death with and without Appropriate Implantable Cardioverter-defibrillator Shocks.

| Medication known | With appropriate ICD shocks | Without appropriate ICD shocks | Total | p value | a vs. b |
|-----------------|-----------------------------|--------------------------------|-------|--------|--------|
|                 | Western (n=23) | Asian (n=3) | Total (n=26) | Western (n=9) | Asian (n=28) | Total (n=37) | Western (n=14) | Asian (n=31) | [a] vs. [b] |
| Diltiazem (mg) | 80±35 | 220±28 | 132±82 | 60 | 206±57 | 190±72 | 72±27 | 208±55 | 0.001 |
| Verapamil (mg) | 93±23 | 0 | 93±23 | 220±75 | 0 | 220±75 | 173±88 | 0 | 1.000 |
| Nifedipine (mg) | 33±6 | 0 | 33±6 | 40±17 | 37±15 | 38±15 | 38±15 | 37±15 | 0.924 |
| Amlodipine (mg) | 10 | 0 | 10 | 10 | 5 | 7±3 | 10 | 5 | 0.095 |
| Benidipine (mg) | 0 | 2 | 2 | 7±4 | 7±4 | 7±4 | 0 | 7±4 | 0.001 |
| ISMN (mg) | 20 | 40 | 33±12 | 60 | 42±15 | 44±15 | 40±28 | 42±13 | 1.000 |
| ISDN (mg) | 80 | 0 | 80 | 43±17 | 40 | 41±9 | 50±22 | 40 | 0.106 |
| Nicorandil (mg) | 10 | 15 | 13±14 | 0 | 17±3 | 17±3 | 10 | 17±3 | 0.137 |
| Nitrate tape (mg) | 0 | 0 | 10±7 | 30 | 10±7 | 10±7 | 0 | 1.000 |
| Amiodarone (mg) | 0 | 100 | 100 | 0 | 114±38 | 114±38 | 0 | 113±35 | 1.000 |

ISMN: isosorbide mononitrate, ISMN: isosorbide dinitrate, ICD: implantable cardioverter-defibrillator
The total population of patients with appropriate ICD shocks in Western and Asian countries.

ICD: implantable cardioverter-defibrillator

Figure 2. The total population of patients with appropriate ICD shocks in Western and Asian countries. ICD: implantable cardioverter-defibrillator

The present study was associated with some limitations. First was a retrospective study. Moreover, there were selection and publication biases in the published papers. Second, the same categorical data were not available to compare each of the issues in all of the 137 patients. We were able to analyze the dosage of calcium channel antagonists or nitrate/nicorandil and coronary risk factors in less than a third of the patients. We tried to analyze these data using a multivariate regression analysis. However, we could not obtain statistically significant results due to the data that were missing in each paper. Further prospective studies will be necessary to investigate the optimal treatments for suppressing the next serious fatal arrhythmia after ICD implantation in patients with aborted SCD due to coronary spasm.

Conclusions

After ICD implantation in patients with aborted SCD due to coronary artery spasm, appropriate ICD shocks were observed in a quarter of these patients during the 41-month follow-up period. Cardiologists should reconsider administering more medications, including two or three calcium channel antagonists, to patients with aborted SCD due to coronary artery spasm as well as ICD implantation.
The authors state that they have no Conflict of Interest (COI).

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