Review

Life-threatening arrhythmias leading to syncope in patients with vasospastic angina

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A B S T R A C T

The coronary artery diseases (CAD) that can lead to the occurrence of a syncopal attack include acute coronary syndrome, vasospastic angina, effort angina, and prior myocardial infarction. The possible mechanisms considered to lead to syncope in patients with CAD are pump failure, tachyarrhythmia, bradycardia, and vagal stimulation. Coronary artery spasm, in particular, is occasionally observed in patients with unexplained syncope in Japan. Life-threatening arrhythmias are among the most serious complications of an ischemic attack caused by coronary spasm, and are associated with an increased risk of syncope and/or sudden cardiac death (SCD). Therefore, during the initial evaluation of unexplained syncope, the diagnosis of vasospastic angina (VSA) needs to be made promptly, to avert the risk of SCD as a consequence of syncope triggered by the lethal arrhythmia. The inducibility of polymorphic ventricular tachycardia or ventricular fibrillation, increased QT dispersion, T-wave alternans, and early repolarization during the asymptomatic period are considered risk markers for ventricular arrhythmias during coronary spasm. In view of the conclusions from several studies, implantable cardioverter/defibrillator therapy should be considered in patients who are at high risk for recurrence of syncope due to a fatal ventricular arrhythmia triggered by coronary spasm, despite appropriate medical therapy.

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1. Introduction

Myocardial ischemia in patients with coronary artery diseases (CAD) increases the risk of syncope. The CAD that can lead to the occurrence of a syncopal attack include acute coronary syndrome, vasospastic angina, effort angina, and prior myocardial infarction. The possible mechanisms considered to lead to syncope in patients with CAD are pump failure, tachyarrhythmia, bradycardia (including sinus arrest and atrioventricular block), and vagal stimulation.

The cause of myocardial ischemia, as well as any signs of previous myocardial infarction, should be evaluated in patients...
with syncope who are at risk of CAD. The treatment and prognosis in patients with syncope due to CAD depend on the existence of a previous myocardial infarction and severely depressed left ventricular function. In patients who have a prior myocardial infarction with reduced ejection fraction (<35%), life-threatening ventricular arrhythmias often develop with the occurrence of syncope. Therefore, an implantable cardioverter/defibrillator (ICD) may be indicated, regardless of the perceived etiology of the event [1,2].

This review summarizes the risk stratification and treatment of syncope in patients with CAD, especially vasospastic angina, in the absence of a previous myocardial infarction.

2. Acute coronary syndrome (ACS)

Patients with an ACS in the absence of chest pain are sometimes encountered and are frequently misdiagnosed [3–5]. According to a multinational, prospective, observational study involving 14 countries, of the 20,881 ACS patients in a previous report, 1763 (8.4%) presented without chest pain. Among these latter patients, 23.8% were not initially diagnosed as having an ACS. The dominant presenting symptoms in the 1763 patients included dyspnea, diaphoresis, nausea or vomiting, and syncope/presyncope. Moreover, syncope or presyncope was observed in 335 patients (19.1%) (Fig. 1). With the exception of diaphoresis, each dominant presenting symptom, especially syncope/presyncope, independently increased the risk of hospital mortality in patients without chest pain [5]. This analysis also showed that ACS patients without chest pain were older and sicker than those with chest pain. Therefore, ACS should be differentially diagnosed in patients who initially present with syncope, which may lead to a reduction in adverse outcomes [3–5].

3. Vasospastic angina (VSA)

Lethal arrhythmias triggered by coronary artery spasm have not been classified as a principal cause of syncope in the European Society of Cardiology's guidelines [6], since patients with VSA are seen less frequently in the United States and Europe than in Japan. However, coronary artery spasm is occasionally observed in patients with unexplained syncope in Japan [7–12]. In Japan, life-threatening arrhythmias are one of the most serious complications of an ischemic attack caused by coronary spasm, and are
3.1. Pathophysiology of syncope in VSA

The pathophysiology of syncope in patients with VSA is considered to include atrioventricular block, sinus arrest, ventricular tachyarrhythmias, pump failure due to left ventricular dysfunction, and vagal stimulation [7–12].

In previous case reports concerning patients with variant angina, complete atrioventricular block and ventricular tachycardia (VT) during ST elevation accompanied by chest pain were recorded during episodes of syncope [7–9]. Back in that era, pacemaker implantation and medications such as isosorbide dinitrate and propranolol were prescribed [8]. The incidence of coronary spasm in patients with syncope is relatively high; vasospasm was induced by an ergonovine test in 22–64% of patients with syncope [11,12].

However, in general, ventricular tachyarrhythmias have been frequently cited as a major cause of syncope encountered in patients with VSA [11,14,18,19].

3.2. Evaluation of syncope in patients with VSA

Syncope can be classified into three categories: reflex syncope, orthostatic hypotension, and cardiac syncope [6]. Especially in Japan, cardiac syncope is occasionally caused by fatal arrhythmia due to coronary spasm in patients with VSA on a substrate of structural disease [11,12,18,19]. We propose a diagnostic flowchart in patients with syncope, specifically a Japanese and Asian version (Fig. 2). We first perform an initial evaluation in an outpatient with syncope. We need to check the patient’s medical history, such as prodrome, position, activity, and so on, and perform a physical examination and a 12-lead ECG. In particular, we need to detect ECG features suggesting arrhythmic syncope. Moreover, orthostatic hypotension can be diagnosed by active standing test, while other structural diseases and tachycardia or bradycardia may be identified using standard examinations (**). On the other hand, when the cause of syncope remains uncertain after the initial evaluation, the next step is to investigate these patients on the basis of clinical features. In the case of VSA, chest pain, while supine and during nighttime, has been associated with syncope. In addition, ECG monitoring, including an implantable loop recorder and an electrophysiological study and coronary arteriography, including acetylcholine provocation, should be carried out in VSA patients with suspected vasospasm-driven arrhythmias.

3.3. Association between life-threatening ventricular tachyarhythmias and syncope in VSA

We investigated the clinical and electrocardiographic characteristics of spontaneous polymorphic VT (PVT) developing during a vasospastic attack and carried out a prospective long-term follow-up [18]. The study included 60 consecutive patients with VSA. Eight patients had at least one episode of PVT during Holter recording, whereas the remaining 52 patients had no VT. During a follow-up period of 73 ± 17 months, the incidence of syncope during the drug-free period was higher in patients with PVT (3 of 8 cases [38%]) than in those without VT (1 of 52 [2%]; p < 0.01). Moreover, there was a significant difference in the incidence of SCD between patients with and without VT (2/8 cases [25%] vs. 0/52 [0%]; p < 0.01). Thus, a significant relationship between syncope or SCD and spasm-induced VT was observed in this study. A representative case with syncope due to coronary artery spasm is illustrated in Fig. 3. This patient had syncope accompanied by the development of PVT during a vasospastic attack. During ECG monitoring, ischemic ST-segment elevation was transiently observed in the same lead after spontaneous termination of the PVT (Fig. 3A). Coronary artery spasm was observed to occur spontaneously in the mid-portion of the right coronary artery and was induced in the mid-portion of the left anterior descending artery and left circumflex artery by an intracoronary injection of acetylcholine. Both coronary spasms were completely relieved after injection of isosorbide dinitrate (Fig. 3B).

One study indicated that the circadian variation of coronary spasm triggering sudden cardiac arrest (SCA) or syncope was different from that inducing typical coronary spastic angina in patients with VSA [19]. More specifically, sudden cardiac arrest and syncope occurred more frequently during daytime, and spontaneous ST changes during daytime were recorded more often in patients with SCA and syncope than in angina-only patients. Moreover, nocturnal angina occurred less frequently in patients with SCA and syncope than in angina-only patients. Therefore, both coronary spasm triggering SCA and coronary spasm triggering syncope had a similar circadian variation. On the other hand, life-threatening ventricular arrhythmia is considered the most important predictor of SCA in patients with VSA [14,17,18]. In consequence, fatal arrhythmia triggered by
coronary spasm may be pathophysiologically associated with syncope as well as SCA [19].

3.4. Risk stratification of ventricular tachyarrhythmia in patients with VSA

Risk stratifications of ventricular arrhythmias, especially lethal arrhythmias, have been clinically evaluated in patients with VSA. Inducibility of PVT or ventricular fibrillation (VF), increased QT dispersion, and T-wave alternans (TWA) during the asymptomatic period are considered risk markers for ventricular arrhythmias during coronary spasm [20–24].

It has been postulated that patients with VSA are likely to have variable electrophysiological instability in the asymptomatic phase, which may be aggravated by ischemic attacks. We evaluated ventricular vulnerability by electrophysiological testing in patients with VSA [20] and found that they had a significantly higher incidence of induced ventricular arrhythmia and VT than those without VSA (Fig. 4). Moreover, patients with VT at baseline electrophysiological testing had a higher incidence of ventricular arrhythmias during vasospastic attack than did those without VT. The incidence of induced ventricular arrhythmias and VT at baseline in VSA patients was significantly higher than that after isosorbide dinitrate. Furthermore, the arrhythmias became significantly less severe after isosorbide dinitrate (Fig. 4). Thus, patients with VSA exhibit increased ventricular vulnerability, even during an asymptomatic phase [20]. This increased vulnerability may predispose them to the development of malignant ventricular arrhythmias aggravated by vasospastic events. One study has reported that VF was most frequently induced by electrophysiological testing in patients surviving out-of-hospital cardiac arrest who had acetylcholine-induced coronary spasm [25]. This study also suggested that induced ventricular arrhythmias were often observed during electrophysiological testing in VSA patients at high risk for life-threatening arrhythmias.

We reported that patients with VSA exhibited an increased baseline QTc dispersion compared to patients with atypical chest pain, which suggests that inhomogeneity of repolarization and susceptibility to ventricular arrhythmias are increased in patients with VSA, even when asymptomatic [21]. Parchure et al. also indicated that QT dispersion is increased in patients with Prinzmetal’s variant angina complicated by cardiac arrest and syncope, compared to patients without such events [23]. However, because modified moving average method (MMA)-TWA analysis has been shown to be a superior measure to QT dispersion for predicting a high risk of ventricular tachyarrhythmia and sudden cardiac death, we analyzed MMA-TWA using Holter recordings in 40 patients with VSA and in 40 control subjects [24]. The incidence of positive TWA (p-TWA) was significantly higher in the VSA group than in the control group (Figs. 5 and 6). The value of the maximum MMA-TWA was also greater in the VSA group than in the control group (68.6 ± 21 vs. 34.0 ± 11 μV, p < 0.01). In the VSA group, although there was no significant difference in maximum MMA-TWA values between patients with multiple- and single-vessel spasm, patients with VT had significantly higher values than those without (Fig. 6). Patients taking calcium channel blockers exhibited lower values of maximum MMA-TWA compared with subjects not taking these drugs (73.8 ± 18 vs. 59.5 ± 21 μV, p < 0.05) [24]. Thus, high values
and incidences of TWA events were observed in patients with VSA. In the VSA group, maximum values of MMA-TWA were high in patients with VT but lower in those taking calcium channel blockers [24]. These results suggest that patients with VSA exhibit repolarization abnormalities during asymptomatic phases, leading to a potential risk of life-threatening arrhythmias.

In addition, several studies have indicated the significance of early repolarization (ER) in VSA patients with fatal arrhythmia [26–28]. Oh et al. indicated that ER could predict cardiac death and fatal arrhythmias in patients with VSA [27]. Kitamura et al. reported that the ER pattern in VSA patients, especially its day-to-day variation, was a good predictor of VF recurrence [28].
report, ER was observed more frequently in patients with a history of VF than in those without. ER was independently associated with VF history. VF recurrence was higher in patients with ER or VF history than in those without. Among the patients with ER, day-to-day variations in ER and notching of the ER pattern were associated with VF history (Fig. 7). Cases with day-to-day variation showed a higher incidence of VF recurrence during follow-up (Fig. 8). Consequently, the investigators concluded that the high prevalence of an ER pattern in VSA patients with a history of VF suggests that its presence is a sign of vulnerability to fatal arrhythmias. The ER pattern, especially its day-to-day variation, can be a good predictor of VF recurrence [28].

It was not known, however, whether the presence of ER could predict life-threatening arrhythmic risk due to repolarization or depolarization abnormalities. To investigate the prevalence of fatal ventricular tachyarrhythmia and the appearance of both ER and p-TWA in VSA during symptom-free periods, we studied 66 patients with a positive acetylcholine test (VSA group) and 50 patients with a negative test (control group) [29]. The presence of ER on the ECG and MMA-TWA during symptom-free periods were explored. We found that the incidences of ER and p-TWA were higher in the VSA than in the control group ($p=0.001$ and $p=0.006$, respectively).

**Table 1**

A comparison of the parameters between the vasospastic angina patients with and without a cardiac event (VF) [29].

|                      | VSA with VF (n=3) | VSA without VF (n=63) | $p$  |
|----------------------|-------------------|-----------------------|------|
| Male (n)             | 3                 | 43                    | 0.031|
| Age (years)          | 50.3 ± 10.3       | 65.8 ± 9.9            |      |
| LVEF(%)              | 61.0 ± 1.0        | 65.3 ± 10.6           | 0.581|
| QRS width (ms)       | 72.7 ± 15.3       | 78.0 ± 11.6           | 0.301|
| QTc (ms)             | 357.7 ± 42.9      | 385.8 ± 35.6          | 0.192|
| Baseline ER (n)      | 3                 | 21                    | 0.019|
| Horizontal/descending (n) | 1             | 7                     | 1.000|
| TWA > 65 μV (n)      | 3(3)              | 15(38)                | 0.042|
| Baseline ER + TWA > 65 μV (n) | 3(3)          | 6(38)                 | <0.001|
| Multivessel (n)      | 3                 | 40                    | 0.195|

LVEF, left ventricular ejection fraction; ER, early repolarization; TWA, T-wave alternans; VF, ventricular fibrillation; VSA, vasospastic angina

**Fig. 7.** Kaplan–Meier survival curves for ventricular fibrillation (VF) among vasospastic angina (VSA) patients with and without day-to-day variation of early repolarization (ER) [28]. Patients with day-to-day variation in their ER pattern had a lower cumulative survival rate after VF than those without.

**Fig. 8.** A series of 12-lead ECG tracings and an intracardiac electrogram from a representative case with recurrence of ventricular fibrillation (VF) during the follow-up period [28]. (A) Twelve-lead ECG recorded 13 h after the first VF episode. Early repolarization (ER) patterns in the lateral leads are visible. (B) ECG without ER pattern 3 days after the first VF episode. (C) ECG with ER pattern 1 month before VF recurrence. (D) ECG with ER pattern after VF recurrence. (E) Intracardiac electrogram from the ICD during VF recurrence. An ICD shock successfully terminated VF.
Multivariate analysis revealed that ER and p-TWA were independent predictors of VSA (odds ratios, 5.65 and 4.94; 95% confidence intervals: 1.11–28.9 and 1.22–19.9, respectively). The incidence of coexisting baseline ER and p-TWA was significantly higher in VSA patients with life-threatening arrhythmic events than in those without (3/3 vs. 6/38; \( p < 0.001 \)) (Table 1) [29]. A representative case who developed VF during the follow-up period is shown in Fig. 9. This patient exhibited p-TWA throughout the follow-up period. Thus, VSA patients with arrhythmic events show a high incidence of ER and p-TWA during symptom-free periods; baseline ER and p-TWA may help to identify VSA patients at high risk for life-threatening arrhythmias [29].

Considering the above clinical reports [18–29], we speculated that the mechanism of fatal ventricular arrhythmia leading to syncope and sudden cardiac death may be as shown in Fig. 10. During the asymptomatic phase, coronary vasoconstriction representing subclinical ischemia already induces increased dispersion of repolarization and depolarization abnormalities, which lead to increased ventricular vulnerability. Furthermore, myocardial ischemia, including silent ischemia, is induced by severe coronary spasm, which aggravates ventricular vulnerability to the development of fatal arrhythmias leading to syncope and SCD. The fatal arrhythmia may be triggered by atrial fibrillation and premature ventricular contractions [17,18]. Here, we emphasize that the presence of ER and p-TWA may be a significant predictor of fatal arrhythmia in VSA.

3.5. Management of syncope in patients with VSA

It has been previously reported that calcium antagonists can prevent SCD and improve the prognosis in patients with VSA [16]. However, with the widespread use of the automatic external
defibrillator (AED), we often encounter VSA patients with VF who were treated appropriately by AED. Lethal arrhythmias triggered by coronary artery spasm are involved as the principal cause of syncope. Syncope due to vasospasm-driven fatal arrhythmias may degenerate into cardiopulmonary arrest in VSA patients. According to the recommendation in the guidelines of the Japanese Circulation Society, ICD therapy for secondary prevention is classified as class IIb in patients who are at high risk for recurrence of fatal ventricular arrhythmia and syncope due to coronary spasm, despite appropriate medical therapy.

We investigated the clinical implications of ICD therapy in 23 patients with VSA and documented lethal arrhythmia [30]. The follow-up period after the first lethal arrhythmic event was 2.9 years (median 2.1 years). All patients were still alive and symptom-free with prescribed medication after ICD implantation. During the follow-up period, 5 patients reached endpoints, including 4 patients with appropriate ICD therapy (Fig. 11) and 1 patient with pulseless electrical activity. The arrhythmias treated by ICD were all VF episodes, which were identified by a review of stored electrocardiograms. All 4 patients with VF were treated appropriately by ICD and resuscitated [30]. One patient presented to hospital with sudden cardiac arrest after chest pain, and the ECG at the emergency department showed pulseless electrical activity. This patient was successfully resuscitated, and is still alive.

There were no statistically significant differences in patient characteristics between the recurrence and non-recurrence groups, including medication, smoking status, and whether the patient was or was not free of symptoms after ICD implantation. These findings indicate that patients with VSA and lethal ventricular arrhythmia are a population at high risk for recurrence of cardiopulmonary arrest, while there is no reliable indicator for predicting the recurrence of ventricular arrhythmia. ICD implantation with medication for VSA is appropriate for this high-risk population [30]. Other reports also supported ICD therapy as secondary prevention in these high-risk patients with VSA [31,32].

In view of these study conclusions [30–32], ICD therapy should be considered in patients who are at high risk for recurrence of syncope due to a fatal ventricular arrhythmia triggered by...
coronary spasm, despite appropriate medical therapy. In these cases, in addition to electrophysiologic testing, the presence of ER and p-TWA—which is a strong risk factor for life-threatening ventricular arrhythmia—in VSA patients—may help to confirm the indication for ICD implantation.

4. Effort angina

True syncope during exercise in patients with effort angina is rare and should be thoroughly evaluated. The causes of syncope that is primarily due to the development of myocardial ischemia are considered to be pump failure, tachyarrhythmia, and bradyarrhythmia, which is a strong risk factor for life-threatening ventricular arrhythmia in VSA patients—may help to confirm the indication for ICD implantation.

Conflict of interest

The author has no conflicts of interest to declare.

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