Polymorphic Ventricular Tachycardia in Patients With Vasospastic Angina

— Clinical and Electrocardiographic Characteristics and Long-Term Outcome —

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There have been few clinical studies exploring the characteristics of spontaneous polymorphic ventricular tachycardia (VT) during a vasospastic angina attack. During a 4-year recruitment period, Holter ECG recordings were monitored for 42±24 h during a drug-free period in 60 consecutive patients with vasospastic angina (VSA) and of these, 8 patients had at least one episode of polymorphic VT during monitoring. Ischemic ST segment elevation was immediately preceded the spontaneous polymorphic VT in all 8 patients, 4 of whom had silent coronary vasospasm. Immediately before the onset of polymorphic VT, both R-on-T and long-short sequences were observed in 4 of the 8 patients and ST wave alternans were recorded in 2 patients. VT exhibited a pattern of torsade de pointes in 4 of the 8 patients. Five patients underwent electrophysiologic testing during a drug-free asymptomatic phase, and polymorphic VT was induced in 2 of the 5 patients, with one developing ventricular fibrillation. During a follow-up period of 73±17 months, there was a significant difference in the incidence of sudden death between patients with and without VT (2/8 cases [25%] vs 0/52 [0%]; $p<0.01$). Thus, vasospastic attacks, even if asymptomatic, that immediately precede the development of polymorphic VT may be associated with a repolarization abnormality and an increased risk of sudden death. (*Jpn Circ J* 2001; 65: 519–525)

Key Words: Coronary artery spasm; Polymorphic ventricular tachycardia; Silent ischemia; Vasospastic angina; Ventricular arrhythmia

The clinical characteristics and mechanism of polymorphic ventricular tachycardia (VT) in the setting of prolonged Q-T interval have extensively been studied^{1–3} but polymorphic VT with normal Q-T interval has infrequently been reported and most reports concern its development in the early stage of acute myocardial infarction^{4,5} Eisenberg et al described 15 patients who exhibited polymorphic VT and normal QT interval in the absence of apparent structural heart disease⁶ and of these he found that only 2 had polymorphic VT during episodes of coronary artery spasm.

Recently, using electrophysiologic studies (EPS) and examination of QT dispersion on 12-lead surface ECG, we reported that patients with vasospastic angina (VSA) exhibit inhomogeneity of ventricular repolarization and increased ventricular vulnerability, even during the symptom-free period.^{7–9} These life-threatening ventricular arrhythmias are one of the most serious complication of ischemic attack caused by coronary spasm, and are associated with an

increased risk of sudden cardiac death!^{10–14} However, to the best of our knowledge, there have been few clinical studies exploring the clinical and electrocardiographic characteristics and prospective long-term follow-up of spontaneous polymorphic VT developing during a vasospastic attack. Therefore, we investigated the characteristics of spontaneous polymorphic VT in patients with VSA and their long-term outcome.

Methods

Patients

The study group comprised 60 Japanese patients with VSA (44 men, 16 women; mean age, 56 years [range, 44–75 years]) consecutively enrolled at Yokohama Minami Kyosai Hospital (single institution) from April 1991 to March 1995. All patients with VSA had a spontaneous episode of angina and coronary vasospasm, defined as total or subtotal (99% with delay) occlusion, or a severe constriction of the vessel associated with myocardial ischemic ST segment changes on ECG and chest pain after the intracoronary injection of acetylcholine. No symptomatic significant coronary stenosis on baseline angiograms and no history of myocardial infarction were noted in any of the 60 patients. None had evidence of cardiomyopathy, congestive heart failure, peptic ulcer, chronic obstructive lung disease or other serious cardiopulmonary diseases. All patients had normal ventricular function without segmental wall motion abnormality on the resting M-mode and 2-dimensional echocardiogram. Doppler echocardiograms revealed no abnormalities in any

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Table 1 Clinical and Electrocardiographic Characteristics of Patients With Polymorphic Ventricular Tachycardia

Patient no.	Age (years) /Sex	Date	Dominant rhythm	QT (ms)	QTc (ms)	Result of coronary arteriography	Site of coronary spasm*	Angina	ST elevation	Interval from ST elevation to onset of PVT
1	36/M	Jul. 91	Sinus	320	410	Normal	LAD(6,8), LCx(12)	+	+	60 s
2	73/M	Nov. 92	AF	340		Normal	LAD(6)	—	+	1 s
3	62/M	Apr. 92	Sinus	360	440	Normal	LAD(6)	—	+	105 s
4	60/M	Oct. 93	Sinus	380	414	Normal	LAD(6)	+	+	135 s
5	67/M	Apr. 93	Sinus	380	380	Normal	LAD(6)	+	+	180 s
6	52/M	Apr. 93	Sinus	420	400	Normal	LAD(8), LCx(13), RCA(2)	+	+	165 s
7	60/M	Nov. 94	AF	400		Normal	LAD(6)	—	+	75 s
8	44/M	Sep. 95	Sinus	400	417	Normal	LAD(7)	—	+	105 s

AF, atrial fibrillation; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; PVT, polymorphic ventricular tachycardia; Tdp, torsade de pointes; ISDN, isosorbide dinitrate; VF, ventricular fibrillation. *Number in parentheses refers to the segment of the coronary artery as defined by the American Heart Association Committee Report!¹⁹

of the patients. The study protocol was approved by the institutional Ethics Committee and all patients gave their written informed consent to participate in the study.

Ambulatory Electrocardiography

Continuous 2-channel ambulatory ECG recordings were monitored for at least 24 h (mean duration, 42±24 h) in all the patients, who had stopped taking antianginal medications, except for sublingual nitroglycerin, at least 3 days prior to the study. The recorder was a frequency-modulated 2-channel Holter monitor unit (Marquett 8500 recorder and Holter analysis system 8000/T or SXP, Marquette Electronics, USA) with 2 exploring electrodes in the V₁ and V₅ sites and 2 negative electrodes to the manubrium. Before the initial recording, the signal from each channel was recorded on a standard ECG with the patient standing, sitting, supine and lying on the left and right sides. The ECG signals were examined to confirm that changes in position did not cause ST segment deviation. The 1-mV calibration signal recorded at the beginning of each tape matched a 10-mm deflection of the recording needle on the recorder. The tapes were scanned for the presence, interval and frequency of ischemic episodes, which were defined as transient ST segment elevation of 1 mm or more from the baseline at 0.08 s after the J point. Polymorphic VT was defined as the rapid (>200 beats/min) tachycardia of more than 10 beats in duration showing continuous changes in the QRS complex. A pattern of torsade de pointes was defined as the rotation of the QRS polarity across the baseline, and the presence of early ventricular beats with a short coupling interval falling on the peak of the T wave or on its ascending limb, within the vulnerable period of the ventricles, at the initiation of VT was defined as an 'R-on-T' tachycardia onset.^{4,15}

Angiography

Coronary arteriography study was carried out using the Judkins technique in the fasting and nonsedated state. Except for sublingual nitroglycerin, all antianginal drugs were discontinued for at least 3 days before the study. None of the patients were taking antiarrhythmic agents. Baseline coronary arteriography was done in the right anterior oblique projection for the left coronary artery and the left anterior oblique projection for the right coronary artery. A bipolar electrode catheter was positioned in the right ventricular apex through the right femoral vein, and connected to a temporary pacemaker set at a rate of 50 beats/min. Incremental doses of acetylcholine were injected into the left coronary artery (20, 50 and 100 µg) and later into the

right coronary artery (20, 50 and 70 µg) until coronary spasm was induced or the maximal dose was attained.^{16,17} Finally, arteriograms were obtained in several projections after the injection of 1.0 mg of isosorbide dinitrate into both the left and right coronary arteries, and the organic coronary artery lesion was evaluated. Surface ECG and arterial blood pressure were continuously monitored during the study. Twelve-lead ECG was recorded at appropriate intervals using radiolucent carbon electrode.

Electrophysiological Study

Programmed electrical stimulation was performed at the right ventricular apex with 1–2 extrastimuli after 8 basic stimuli with cycle lengths of 600 and 400 ms.^{7,18} The end-point for programmed stimulation^{7,18} was either induction of sustained VT or ventricular fibrillation or completion of the pacing protocol with 2 extrastimuli. VT was defined as nonsustained if the tachycardia lasted 6 beats and terminated spontaneously in less than 30 s. Sustained VT was defined if the tachycardia lasted for more than 30 s or required quick termination because of hemodynamic compromise. Polymorphic VT was defined as the tachycardia showing continuous changes in the QRS morphology on the surface ECG. Ventricular fibrillation was defined as a rapid polymorphic tachycardia without a clear distinction between QRS and T waves and with hemodynamic deterioration that required a prompt resuscitation.

Follow-up

Patients were followed up at regular intervals by the cardiology clinic. All patients were taking calcium channel blocker and/or long-acting isosorbide dinitrates during the follow-up period. Follow-up ECG and 24-h Holter recordings were obtained twice yearly. Patients were followed for a mean of 73 months (range, 45–95).

Statistical Analysis

Data are expressed as a mean value ± SD. The difference in incidence of syncope and sudden death between the patients with and without polymorphic VT was analyzed by Fisher's exact probability test or chi-squared test. A *p* value less than 0.05 was considered statistically significant.

Results

Polymorphic Ventricular Tachycardia During Ambulatory Monitoring

Of the 60 patients, 8 had at least one episode of polymor-

<i>R on T</i>	<i>Long-short sequence</i>	<i>T wave alternans</i>	<i>Tdp</i>	<i>Follow-up period (months)</i>	<i>Medication</i>	<i>Outcome</i>	<i>Cause of death</i>
+	+	+	+	95	Diltiazem 90 mg, nicorandil 15 mg	Survived	
-	-	-	-		Nifedipine 40 mg, ISDN 60 mg	Died at 5 months	VF
+	+	-	+	86	Nifedipine 40 mg, ISDN 60 mg	Survived	
-	+	+	-	68	Diltiazem 90 mg, ISDN 60 mg	Survived	
+	-	-	-	74	Diltiazem 120 mg, ISDN 60 mg, nicorandil 15 mg	Survived	
-	-	-	-	74	Diltiazem 90 mg, nifedipine 40 mg, ISDN 80 mg	Survived	
+	+	-	+		Diltiazem 90 mg, ISDN 60 mg	Died at 18 months	VF
+	+	-	+	45	Diltiazem 120 mg	Survived

Fig 1. (A) Ambulatory ECG monitoring of patient no. 2 during a painless vasospastic attack. Rapid polymorphic VT, which spontaneously reverted to atrial fibrillation, was recorded for 45 s while sleeping. (B) Electrogram at onset and termination of polymorphic VT with enlarged time scale. Ischemic ST segment elevation at 2 heart beats (large arrows) in channel 2 (CM5) lead immediately precedes the onset of rapid polymorphic VT (*). Moreover, ST segment change mimicking ST segment elevation was observed during the 1st, 2nd and 4th beats (second panel of Fig 1A). Ischemic ST segment elevation was still observed in the same lead after the spontaneous termination of VT (**).

phic VT of more than 10 beats during monitoring (Table 1). Patients with polymorphic VT had a higher incidence of syncope during the drug-free period (3 of 8 cases [38%]) than those without VT (1 of 52 [2%]; $p < 0.01$).

One patient (no. 2) had polymorphic VT during a painless vasospastic attack. During 24-h ambulatory monitoring, ischemic ST segment elevation in 2 heart beats at the channel 2 (CM5) lead immediately preceded the development of rapid polymorphic VT (Fig 1) and was still observed in the same lead after the spontaneous termination of VT. Coronary artery spasm was induced in the midportion of the left anterior descending artery by the intracoronary injection of acetylcholine (Fig 2).

Another patient (no. 3) had 3 episodes of ischemic ST elevation during 24-h ambulatory monitoring, of which 2 were not accompanied by chest pain. Spontaneous polymorphic VT with a pattern of torsade de pointes was recorded

Fig 2. Coronary angiogram in the right anterior oblique projection in the patient no. 8 at baseline and after injection of acetylcholine. Subtotal occlusion was induced in the midportion of the left anterior descending artery, but was not accompanied by chest pain.

Fig3. Ambulatory ECG monitoring of patient no.3 during an asymptomatic vasospastic attack while sleeping. Spontaneous polymorphic VT with a pattern of torsade de pointes was recorded with ST segment elevation. Both R-on-T and long-short sequence of the QRS were recorded at the onset of polymorphic VT.

during the painless vasospastic attack (Fig 3). Both R-on-T and long-short sequence of the QRS on ECG were recorded at the onset of polymorphic VT. Total occlusion in the proximal portion of the left anterior descending artery was induced by the intracoronary administration of acetylcholine (Fig 4).

Ischemic ST segment elevation immediately preceded the development of spontaneous polymorphic VT in all 8 patients, in 4 of whom chest pain did not accompany the ECG changes. The time that elapsed from the onset of ST segment elevation on the ECG to the onset of polymorphic VT was 1.0 s to 3.0 min (average, 2.5 ± 0.5 min). The dominant rhythm was sinus rhythm at baseline in 6 of the 8 patients, and atrial fibrillation in the remaining 2. Spontaneous conversion of polymorphic VT to baseline rhythm was observed 3–45 s after onset of VT. The QT interval was normal in all patients. Immediately before the onset of polymorphic VT, both R-on-T and long-short sequence of the QRS on ECG monitoring occurred in 4 of the 8 patients, and one or other of these changes was recorded in the remaining 2 patients. A pattern of torsade de pointes was observed in 4 of the 8 patients, who were included in the general category of polymorphic VT, and ST wave

Fig5. Ambulatory ECG monitoring of patient no.4 during a vasospastic attack. ST wave alternans was recorded during ST elevation (arrow), and at 2 min 15 s after the onset of ST segment elevation, polymorphic VT appeared with a long-short sequence of the QRS.

Fig4. Coronary angiogram in the right anterior oblique view and ECG of patient no.3 after injection of acetylcholine and isosorbide nitrate (ISDN). Total occlusion in the proximal portion of the left anterior descending artery was induced by acetylcholine and ischemic ST segment elevation in leads V1 and V3 were recorded immediately before arteriography.

alternans was recorded during episodes of ischemic ST elevation in 2 patients (Fig 5). None of the patients had sinus bradycardia. No abnormality of serum potassium and calcium levels at baseline were noted.

Induction of Coronary Spasm With Acetylcholine

At baseline, 2 patients (nos. 1 and 5) had a mild spontaneous vasoconstriction in the left anterior descending artery with less than 25% stenosis of the luminal diameter. None of these patients had accompanying symptoms. One patient (no. 6) had a high degree of vasoconstriction in the right coronary artery with 75% stenosis, but no ischemic ECG change or chest pain was noted. The remaining 5 patients had normal coronary arteries at baseline.

After injection of acetylcholine, coronary artery spasm in 1 vessel was induced in 6 patients and spasms in 2 vessels occurred in the other 2. Total occlusions were induced in 6 vessels of 6 patients and subtotal occlusion in 3 vessels of 3 patients. All patients exhibited normal coronary arteriograms after isosorbide dinitrate (Table 1).

During the induction of coronary spasm by acetylcholine, ventricular arrhythmias were observed in 4 of the 8 patients. Two of the 4 patient had at least 3 consecutive ventricular premature beats.

Electrophysiological Study

Five of the 8 patients with spontaneous polymorphic VT underwent an EPS during the drug-free asymptomatic phase. Polymorphic VT lasting at least 6 consecutive ventricular premature beats was induced in 2 of the 5 patients, with one patient developing ventricular fibrillation, but the remaining 3 did not develop VT.

Patient no. 6, who had induced polymorphic VT that degenerated rapidly into ventricular fibrillation (Fig 6), had focal vasoconstriction in the right coronary artery with 75% stenosis after cardioversion as well as during the baseline angiography (Fig 7). Total occlusion in the midportion of the left anterior descending artery and the right coronary artery, and subtotal occlusion in the midportion of left circumflex artery were induced by acetylcholine (Fig 7). After isosorbide dinitrate which completely resolved the coronary spasms, nonsustained polymorphic VT with stable hemodynamic parameters was reproducibly induced by 2 extrastimuli.

Fig6. Surface and intracardiac ECGs recorded in patient no. 6 during programmed ventricular stimulation in the baseline asymptomatic phase. As the coupling interval was reduced from 200 to 190 ms, rapid polymorphic VT was induced reproducibly at a cycle length of 400 ms with 2 extrastimuli and degenerated rapidly into ventricular fibrillation. RVA, right ventricular apex; Ao, aortic pressure.

Follow-up

During a follow-up period of 73 ± 17 months, there was a significant difference in the incidence of sudden death between patients with and without polymorphic VT (2/8 cases [25%] vs 0/52 [0%]; $p < 0.01$). Patients no. 2 and no. 7 died suddenly from ventricular fibrillation at 5 and 18 months, respectively, during the follow-up period.

Discussion

The present study demonstrated that a significant number of patients with VSA (8/60 cases) developed spontaneous episodes of polymorphic VT during Holter monitoring, and some of them were not accompanied by chest pain (silent ischemia). Most of the VT attacks were preceded by ST alternans, and long-short sequence of the initiating premature ventricular beat. These 8 patients had a high incidence of VT induced by programmed ventricular stimulation during their asymptomatic period, suggesting that the risk of sudden cardiac death was high in these patients.

Possible Mechanism of Spontaneous Polymorphic VT During Coronary Spasm

Myocardial ischemia during coronary spasm may generate electrophysiologic derangement leading to serious ventricular arrhythmias, but the prospective evaluation of the functional substrate under such condition is difficult and it is perhaps harmful to perform the assessment test during the patient's unstable condition, compared with cases of old or healed myocardial infarction.^{18,20-24}

Studies of polymorphic VT associated with acute myocardial infarction have disclosed that the QT interval is normal in most cases,^{4,5} which can be explained by localized and regional differences in repolarization or focal afterdepolarizations. In the present study, the baseline QT interval in all cases was normal, but the QT interval on

Fig7. Coronary arteriogram in patient no. 6 with multivessel coronary spasm after injection of acetylcholine. Focal vasoconstriction in the right coronary artery (RCA) with 75% stenosis was observed during baseline angiography. Total occlusion in the midportion of the left anterior descending artery and the RCA and subtotal occlusion in the midportion of left circumflex artery were induced by acetylcholine. Coronary spasm was completely relieved after isosorbide dinitrate. LCA, left coronary artery; RAO, right anterior oblique; LAO, left anterior oblique.

surface ECG immediately before development of polymorphic VT, was not obtained and, therefore, the QT intervals during vasopastic attacks were not evaluated. In fact, as spontaneous coronary spasms occur briefly and with variable duration, it is difficult to evaluate the disparity of ventricular repolarization during the spasm.

Recently, using EPS and QTc dispersion on the 12-lead ECG, we showed that inhomogeneity of ventricular repolarization in asymptomatic patients with VSA is one of the important predictors of ventricular arrhythmias during induced coronary spasm.⁷⁻⁹ In the present study, 4 cases of polymorphic VT showed a pattern of torsade de pointes, which was frequently encountered in the presence of a prolonged QT interval. The polymorphic VT with a torsade de pointes pattern was infrequently noted with normal Q-T interval in the early stage of an acute myocardial infarction.⁴ In the present study, ST wave alternans and long-short sequence of the QRS without QT prolongation was often recorded before the onset of VT, suggesting increased dispersion of ventricular repolarization. ST alternans is frequently observed in severe myocardial ischemia and is known to be a predictor of life-threatening ventricular tachyarrhythmias.²⁵⁻²⁷ It is also a hallmark of repolarization abnormality leading to reentry.²⁸⁻³⁰ Therefore, an abnormality of ventricular repolarization may be aggravated by ischemic attack caused by coronary spasm, providing the basis for the development of polymorphic VT.³¹⁻³³

Relationship Between Spontaneous Polymorphic VT and Induced VT

There have been few clinical studies using EPS to explore the risk of ventricular arrhythmias in patients with VSA. In particular, the relation between spontaneous VT and induced VT has not been elucidated. Myerburg et al reported one case in which ventricular flutter was induced by ventricular stimulation in a survivor of sudden cardiac death, but details of the procedure, such as the total number of study patients and the incidence and types of induced arrhythmias, were not described.¹⁴ Therefore, the patho-

physiological significance of the response is unknown.

We recently reported that polymorphic VT was often induced during EPS during the asymptomatic phase in patients with VSA and that patients with ventricular arrhythmias during induced coronary spasm had a high incidence of VT induced by programmed stimulation.⁸ Here we evaluated ventricular vulnerability by programmed ventricular stimulation in 5 patients with spontaneous VT at baseline who did not have any sign of myocardial ischemia. Consequently, polymorphic VT was induced in 2 of the 5 patients, with 1 patient developing ventricular fibrillation. These VT appeared to be determined by the degree of preexisting electrical instability, according to our previous study.⁸ Therefore, we assume that increased ventricular vulnerability during the asymptomatic phase without ischemic attack could predispose to the development of spontaneous polymorphic VT aggravated by a vasospastic attack.

Polymorphic VT Caused by Silent Coronary Spasm and Long-Term Outcome

During monitoring, ischemic ST segment elevation immediately preceded the development of spontaneous polymorphic VT in all 8 patients, 4 of whom had silent coronary spasm. Notably, 2 cases (nos. 2 and 7) who died suddenly from ventricular fibrillation during the follow-up period, had atrial fibrillation as the dominant rhythm and silent vasospastic attacks. Myerburg et al reported that 4 of 5 survivors of sudden cardiac death with ventricular fibrillation caused by silent coronary spasm had had atrial fibrillation after ventricular defibrillation.¹⁴ We assume that dispersion of ventricular repolarization is associated with atrial fibrillation in these patients because of variable R-R intervals and will therefore increase in the patients with rather than those without atrial fibrillation, even in the absence of ischemia.

Patients with VSA frequently have silent vasospastic attacks.^{14,34–36} Chevalier et al reported that 7 patients, recruited retrospectively from a cohort of survivors of cardiac arrest, all had coronary spasm and no history of angina pectoris.³⁷ During monitoring, 4 of their 8 cases had silent ST segment elevation caused by coronary vasospasm. Two of these 4 cases later died suddenly from ventricular fibrillation. Therefore, as in the present study, patients experiencing malignant ventricular arrhythmias with silent myocardial ischemia are at high risk for sudden death.

Study Limitations

Only 8 patients with polymorphic VT of more than 10 beats duration during Holter monitoring were followed up long term. Moreover, EPS was carried out in 5 of these 8 patients. Therefore, we could not identify statistically a marker for the occurrence of polymorphic VT and sudden cardiac death in patients with VSA. However, in our previous study, patients with ventricular arrhythmias during induced coronary spasm had increased QT dispersion on 12-lead ECG and a high incidence of VT induced by electrophysiologic testing. Moreover, no previous studies have elucidated electrocardiographically polymorphic VT in such patients nor its prospective relation to the susceptibility to sudden cardiac death.

We administered isosorbide dinitrate before the provocative study in the right coronary artery in 2 patients (nos. 5 and 7), because of hemodynamic compromise during induction

of coronary vasospasm in the left anterior descending artery. Therefore, these patients may have had multivessel spasm, which may be an important prognostic factor in patients with VSA.¹³

Clinical Implications

Polymorphic VT caused by vasospastic attack was frequently recorded in patients with VSA and was linked to an ECG finding compatible with an abnormality of ventricular repolarization. Our observations suggest that the patients with VSA have an arrhythmogenic substrate with an increased disparity of ventricular repolarization provoked by myocardial ischemia. Polymorphic VT occurring during silent coronary spasm is a high risk for sudden cardiac death, so patients with VSA need close and careful follow-up.

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