Clinical and Electrocardiographic Characteristics of Electrical Storms Due to Monomorphic Ventricular Tachycardia Refractory to Intravenous Amiodarone

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Background: Few reports are available on the characteristics of electrical storms of ventricular tachycardia (VT storm) refractory to intravenous (IV) amiodarone.

Methods and Results: IV-amiodarone was administered to 60 patients with ventricular tachyarrhythmia between 2007 and 2012. VT storms, defined as 3 or more episodes of VT within 24 h, occurred in 30 patients (68±12 years, 7 female), with 12 having ischemic and 18 non-ischemic heart disease. We compared the clinical and electrocardiographic characteristics of the patients with VT storms suppressed by IV-amiodarone (Effective group) to those of patients not affected by the treatment (Refractory group). IV-amiodarone could not control recurrence of VT in 9 patients (30%). The Refractory group comprised 5 patients with acute myocardial infarctions. Although there was no difference in the VT cycle length, the QRS duration of both the VT and premature ventricular contractions (PVCs) followed by VT was narrower in the Refractory group than in the Effective group (140±30 vs. 178±25 ms, P<0.01; 121±14 vs. 179±22 ms, P<0.01). In the Refractory group, additional administration of IV-mexiletine and/or Purkinje potential-guided catheter ablation was effective.

Conclusions: IV-amiodarone-refractory VT exhibited a relatively narrow QRS tachycardia. The narrow triggering PVCs, suggesting a Purkinje fiber origin, may be treated by additional IV-mexiletine and endocardial catheter ablation.  (Circ J 2015; 79: 2130–2137)

Key Words: Amiodarone; Catheter ablation; Electrical storm; Purkinje potential; Ventricular tachycardia

The efficacy of intravenous (IV) amiodarone is established in patients with shock-resistant ventricular fibrillation (VF) or hemodynamically destabilizing ventricular tachycardia (VT). IV-amiodarone is also well established as a preventive treatment for repetitive forms of VT/VF, including electrical storms refractory to multiple anti-arrhythmic drugs. However, no strategies have been shown on how these lethal arrhythmias should be treated if IV-amiodarone is not effective.

Previous small, nonrandomized trials demonstrated that IV-amiodarone was a safe and effective treatment for suppressing VT/VF. Although the recurrence rate of VT/VF treated by IV-amiodarone was more than 30%, those trials did not report the characteristics of IV-amiodarone-refractory VT/VF in detail. Furthermore, 3 controlled, prospective trials demonstrated that the recurrence rates of VT/VF treated by IV-amiodarone were much higher than those of the previous small nonrandomized trials (54–74% vs. 37–53%). Although
the recurrence of VT/VF leads to a worse outcome, so far little information is available on the characteristics of IV-amiodarone-refractory VT/VF and the therapeutic strategy is unclear. Because the antiarrhythmic effects are expressed slowly and take approximately 24h, it is difficult to evaluate the effectiveness in emergency settings where delayed treatment is not accepted. Therefore, we studied a repetitive and stable form of arrhythmia; that is, electrical storms of hemodynamically tolerated monomorphic VT (VT storms). The purpose of this study was to evaluate the incidence, clinical features, and treatment of IV-amiodarone-refractory VT storms.

Methods

Study Population
IV-amiodarone was administered to 60 patients with VT/VF between 2007 and 2012 in the intensive care unit (ICU) of Nippon Medical School Hospital. Of those, we studied 30 patients with VT storms, defined as 3 or more episodes of monomorphic VT within the 24h before the administration of IV-amiodarone. The mean age was 68±12 years, and the male-to-female ratio was 23:7. The underlying heart diseases were dilated cardiomyopathy (DCM) in 9, acute myocardial infarction (MI) in 6, prior MI in 6, dilated phase of hypertrophic cardiomyopathy (d-HCM) in 5, aortic valve stenosis (AS) in 2, and post-resuscitative state of cardiopulmonary arrest (CPA) in 2 patients. Of those, 15 patients had undergone implantable cardioverter-defibrillator (ICD) implantation before their study inclusion. In 7 of these 15 patients, ICDs were implanted for secondary prevention of sudden cardiac death. All patients gave written informed consent and the protocol was approved by the institutional review board.

ECG Monitoring and Data Measurements
All patients were evaluated in the ICU with continuous ECG monitoring. Either a 2-lead continuous monitor ECG (n=6) or 12-lead ECG (n=24) during the VT storm was recorded for all the study patients before the initiation of the IV-amiodarone. VT was defined as a wide QRS tachycardia with atrioventricular dissociation, which was terminated with ICD therapy, or lasted >30s.12 Monomorphic VT meant that the waveforms of all heart beats matched each other in each of the surface ECG leads. VT was considered hemodynamically stable if the systolic blood pressure (BP) during the VT was >80 mmHg. If IV-amiodarone was used in 5 patients. If IV-amiodarone was administered as a bolus infusion of 125 or 150 mg over 10min followed by a continuous infusion of 50mg/h for 6h (loading period) and then 25mg/h (maintenance period) according to the method described by Katoh et al.11 If the VT persisted during the loading period of the IV-amiodarone, the patient was electrically shocked. If judged necessary, an additional infusion (125 or 150 mg) was permitted in the 24h after the initiation of IV-amiodarone.

Failure of IV-amiodarone to suppress the VT storm was defined as sustained VT recurring over 24h during continuous infusion of IV-amiodarone by a slight modification of the method according to Levine et al.

Treatment Protocol and Additional Therapies for VT Storms
Adding conventional therapies, except for additional medications, was permitted according to necessity within the 24h of initiating IV-amiodarone. All patients with an acute MI had undergone successful percutaneous coronary intervention (PCI) before the VT storm. Repeat coronary angiography (CAG) was performed during the VT storm to exclude any residual ischemia and to confirm no restenosis of the coronary artery in all patients with an acute MI. Electrolyte abnormalities ([K] <4.0mEq/L, [Ca] <8.5mg/dL, [Mg] <1.4mEq/L) were corrected in all patients. Deep sedation with tracheal intubation was performed in 7 patients and of them, 2 patients were on extracorporeal membrane oxygenation (ECMO). Intraaortic balloon pumping (IABP) for maintaining systolic BP (>80mmHg) was used in 5 patients. If IV-amiodarone was considered to be ineffective, temporary overdrive pacing (n=3), additional administration of mexiletine (n=3), and catheter ablation (n=4) were indicated according to necessity.

Statistical Analysis
The clinical and ECG characteristics were compared between the patients with VT storms suppressed by IV-amiodarone (Effective group) and those with VT storms refractory to IV-amiodarone (Refractory group). All quantitative variables are shown as the mean±standard deviation and were compared between groups using Student’s unpaired t-test. The categorical variables are shown as absolute values and percentages, and were assessed with a chi-square test or Fisher exact test as appropriate. Values of P<0.05 were considered significant. The statistical analyses were performed using SPSS Statistics 22 software (IBM Corporation, Armonk, NY, USA).

Results
Recurrence Rate of VT
VT recurred in 9 (30%) patients with acute MI (n=5), d-HCM (n=2), AS (n=1), or CPA (n=1), and IV-amiodarone controlled the recurrence of VT in 21 (70%) patients. The baseline clinical characteristics are shown in Table I. The NYHA functional class, BNP level, and medications did not differ between the Refractory and Effective groups. In 5 of 6 patients with an acute MI, IV-amiodarone-refractory VT occurred 3–13 days after PCI, but repeat CAG revealed no restenosis or additional coronary events. Similarly, a patient with AS developed a VT storm 3days after undergoing aortic valve replacement, and a d-HCM patient with severe MR in the Refractory group developed a VT storm 8 days after mitral valve replacement. The remaining 2 patients in the Refractory group developed VT
storms because of exacerbation of heart failure. The Effective group comprised 9 patients with DCM. Exacerbation of heart failure was the main triggering factor of the VT storms in the Effective group and the mean EF in the Effective group was lower than that in the Refractory group (22.2±8.6 vs. 44.4±20.1, P<0.01). An ICD was implanted in 13 (62%) patients in the Effective group and in 2 (22%) in the Refractory group.

ECG Characteristics
The ECG characteristics of the patients are shown in Table 2. There was no difference in the QT and QTC intervals during sinus rhythm between the 2 groups. In 19 patients, the QRS morphology of the VT was a right bundle branch block (RBBB) pattern. There was no difference in the incidence of RBBB pattern between the 2 groups. Although there was no difference in the CL of the VT, the QRS duration during the VT in the Refractory group was significantly narrower than that in the Effective group (Figure 1). Furthermore, the QRS duration of the triggering PVCs in the Refractory group was much narrower than that in the Effective group (Figure 2). Representative cases are shown in Figure 3. The 12-lead ECGs of the triggering PVCs in the Refractory group revealed a narrow QRS complex with a sharp initial deflection.
Additional Therapies for IV-Amiodarone-Refractory VT Storms

IV-amiodarone-refractory VT storms occurred regardless of whether tracheal intubation with deep sedation, ECMO, and/or IABP was used (Table 3). In 3 patients in the Refractory group, additional administration of IV-mexiletine suppressed the VT storm. IV-mexiletine was administered as a bolus infusion of 125 mg and followed by a continuous infusion of 3 or 6 μg·kg⁻¹·min⁻¹ until catheter ablation (n=2) or non-cardiac death (n=1) occurred. The PVCs immediately disappeared during infusion of IV-mexiletine without any adverse events. In the 4 patients who underwent catheter ablation, Purkinje potential-guided ablation was effective. Purkinje potentials preceding the QRS complex during PVCs were detected and radiofrequency delivery at the sites where the earliest Purkinje potentials were detected resulted in successful ablation. However, in the 5 patients in the Effective group who underwent an electrophysiological study (EPS) and catheter ablation after the study period, the triggering PVCs originated from damaged myocardium and the mechanism of the VT was scar-related reentry.

Adverse Events and Final Outcomes

During the administration of IV-amiodarone, the incidence of
hypotension (defined as a 25% decrease in the systolic BP or BP < 80 mmHg) was 20%. Four (13%) patients developed bradycardia, defined as a heart rate < 50 beats/min. No patients discontinued IV-amiodarone because of adverse events.

After the study period, 4 (25%) patients in the Refractory group died from non-cardiac causes (sepsis in 3, cerebral infarction in 1). In the Effective group, 4 (19%) patients died from renal failure, hemorrhage shock, pneumonia, and sepsis, respectively.

**Discussion**

To the best of our knowledge, this is the first evaluation of the clinical and ECG characteristics of electrical storms due to monomorphic VT refractory to IV-amiodarone. Our study had 3 main findings: (1) the incidence of IV-amiodarone-refractory VT storms was 30%; (2) IV-amiodarone-refractory VT storms were induced by triggering PVCs with a narrow QRS complex, which often occurred following PCI for acute MI or open-heart surgery for cardiac valvular disease; and (3) the VT storms could be suppressed with additional administration of IV-mexiletine and/or Purkinje potential-guided catheter ablation.

The incidence of IV-amiodarone-refractory VT storms in the present study was 30%, which is in agreement with the previous small studies (37–53%).

We speculate that our result was related to the dosage and duration of the administration of IV-amiodarone and also to the number of patients with acute MI. In the previous dose-ranging study, Scheinman et al. reported that the recurrence rate of VT/VF in the 125-mg dose group and 1,000-mg dose group was 84% and 74%, respectively. Even in the high-dose group, the recurrence rate was relatively high because the population with coronary artery disease, and especially acute MI, was high (80% and 13%, respectively). Nalos et al. reported that the recurrence rate of VT/VF was only 9% in their study in which the population did not include patients with acute MI.

On the other hand, in a previous large study, Levine et al. reported that the response to IV-amiodarone was not related to the etiology of the heart disease. However, they did not discriminate acute MI from other coronary artery disease. Although the patients in the present study had a different severity of disease than in the previous studies that included hemodynamically collapsed VT and VF, a large number of patients with acute MI was associated with the incidence of IV-amiodarone-refractory VT storms. VT/VF storms caused by acute ischemia, which may be considered to be refractory to multiple medications, should be treated with revascularization therapy. Hence, we performed repeat CAG during the VT storms, which revealed no residual ischemia. Successful PCI was performed in all patients with acute MI before the study period, and the IV-amiodarone-refractory VT storms, which occurred in the subacute phase of the MI, might have been associated with reperfusion injury rather than with acute ischemia.

VT storms refractory to IV-amiodarone exhibited a relatively narrow QRS tachycardia. Furthermore, the triggering PVCs followed by VT also had a very narrow QRS complex. The mean QRS duration of the triggering PVCs in the Refractory group was 121 ms, suggesting a Purkinje origin. The results of catheter ablation in those patients revealed that the PVCs originated from the Purkinje network. This result coincides with the fact that reperfusion injury-induced arrhythmias in patients with acute MI are strongly associated with the

**Figure 3.** Representative 12-lead ECGs during a ventricular tachycardia (VT) storm. Each 12-lead ECG shows a beat during sinus rhythm and a triggering premature ventricular contraction (PVC) followed by VT. Each PVC exhibits a QRS duration of 140, 120, 180, and 160 ms for cases 24, 25, 11, and 20, respectively. In the Refractory group (cases 24 and 25), the QRS duration of the triggering PVCs, which have a sharp initial deflection, is much narrower than that of the VT itself. Refractory group, unaffected by intravenous amiodarone.
Purkinje network.\textsuperscript{15,16} One of the reasons why Purkinje network-mediated arrhythmias are refractory to IV-amiodarone may be the weak effect of amiodarone on the refractoriness of the His-Purkinje system.\textsuperscript{17,18} In fact, IV-amiodarone might not be effective and catheter ablation would be required in patients with other His-Purkinje network-associated arrhythmias such as idiopathic left fascicular VT or bundle branch reentrant VT. Although the reason why Purkinje network-mediated arrhythmias are refractory to IV-amiodarone is still not clear, the main reason for IV-amiodarone-refractory VT storms is Purkinje arrhythmias occurring after PCI for acute MI.

In 30% of patients with VT storms treated by IV-amiodarone in the present study, additional therapeutic strategies were required to inhibit the IV-amiodarone-refractory VT storms. Deep sedation, overdrive pacing, and mechanical support (IABP, ECMO) were additional options; however, they had only temporary effects. Catheter ablation targeting Purkinje-mediated PVCs may be a definitive therapy.\textsuperscript{19,22} However,
most patients need to be treated more quickly in the emergency setting of an electrical storm. Additional administration of IV-mexiletine can be performed easily and is effective in suppressing IV-amiodarone-refractory VT storms, at least until catheter ablation can be performed.

There are 3 possible effects of mexiletine that explain why additional IV administration was effective for IV-amiodarone-refractory VT storms. First, class I agents such as mexiletine may increase the antiarrhythmic effect of amiodarone on suppressing PVCs originating from the Purkinje network. Reperfusion often leads to the development of automaticity or delayed afterdepolarizations originating from the Purkinje network. Sodium channel blockade is important in regulating the occurrence of these arrhythmias. Although amiodarone’s multichannel blocking effects suppress VT and PVCs originating from damaged myocardium in patients with structural heart disease, its effect on the sodium channels of the Purkinje network is modest. Hence, additional administration of mexiletine can increase the sodium channel blockade effect and a combination of IV-amiodarone and IV-mexiletine might suppress triggering PVCs originating from both the myocardium and Purkinje network. Second, mexiletine may suppress the proarrhythmic effects of amiodarone. Class III agents such as amiodarone can lengthen the action potential duration and repolarization, thus causing a drug-induced form of long QT syndrome. Mexiletine inhibits the late component of the inward sodium current (INa) and shortens the action potential duration. Additional administration of agents that block the late INa current suppresses the QT-prolonging effects of class III agents. Finally, class Ib drugs such as mexiletine may be cardioprotective during ischemic conditions, via opening of the adenosine triphosphate-sensitive potassium channels (KATP). KATP openers protect myocardial cells from ischemia-induced and reperfusion-induced injury by preventing calcium overload during ischemia.

Our results may be applicable to oral therapy. Several researchers have reported that a combination of oral antiarrhythmic drugs used empirically in patients and the complementary actions of class I and class III agents were effective. Gao et al have reported that oral mexiletine can be effective as an adjunctive therapy to oral amiodarone in reducing appropriate ICD therapies in patients who failed on amiodarone therapy alone. However, those researchers gave little information on why additional administration of mexiletine to amiodarone was effective. They did not evaluate the ECG characteristics. Unstable arrhythmias, which need emergency shocks and/or cardiopulmonary resuscitation, do not allow for clarifying the relationship between the ECG findings and response to IV-amiodarone. Our study group comprised only hemodynamically stable patients with monomorphic VTs; hence, we could collect ECG data during VT storms and showed that the QRS duration of the triggering PVCs was associated with the ineffectiveness of IV-amiodarone.

**Study Limitations**

First, the present study was a small, retrospective, and nonrandomized trial because the population with VT storms was very small and the random assignment of patients to an additional treated group would be unethical. Although the data are retrospective and limited, we could detect a relationship between a high incidence of IV-amiodarone-refractory VT storms and narrow QRS duration of the PVC/VT, suggesting a Purkinje origin. The second limitation was that the relationship between QRS duration and the origin of the PVCs and the mechanism of the VT were determined by an EPS in only 9 patients. The QRS duration of the PVC/VT depends on ventricular conduction abnormalities. If a patient has an intraventricular conduction delay during sinus rhythm, the QRS duration widens and this delayed conduction may lead to a relatively wide QRS tachycardia even if the VT originates from the Purkinje network. Similarly, rate-dependent conduction delays might have prolonged the QRS duration in the Effective group. However, in the 9 patients who underwent an EPS, the rate-dependent increase in the QRS duration during incremental pacing was minimal. Third, 12-lead ECG recordings during VT were missed in 6 patients, in whom the QRS duration was measured by 2-lead ECG. In such patients, the QRS duration might differ from that measured by 12-lead ECG. However, the maximum dispersion of the QRS duration in the 12-lead ECG is reported to be between 24 and 48 ms, which is smaller than the difference in the QRS duration between our study groups.

**Conclusions**

Amiodarone-refractory VT and its triggering PVCs have relatively narrow QRS complexes, suggesting a Purkinje fiber origin. Purkinje potential-guided catheter ablation is effective. Additional administration of IV-mexiletine might be a therapeutic option for the treatment of IV-amiodarone-refractory VT storms.

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**Disclosures**

The authors have no conflicts of interest to report related to the present study.

**References**

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