Electrophysiologic Study-Guided Amiodarone for Sustained Ventricular Tachyarrhythmias Associated With Structural Heart Diseases

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Background Although an electrophysiologic study (EPS) and Holter-monitoring are often helpful in evaluating the efficacy of antiarrhythmic drugs in patients with ventricular tachyarrhythmias (ventricular tachycardia/fibrillation (VT/VF)), the efficacy of EPS- or Holter-guided oral amiodarone therapy in Japanese patients is still unclear.

Methods and Results EPS was performed 1 month after starting amiodarone, and Holter-monitoring was recorded before and 1 month after amiodarone in 188 patients with sustained VT/VF because of structural heart diseases. In spite of the judgment of EPS (n=89) or Holter (n=75), all patients continued amiodarone. Patients were followed up to 3 years and the primary endpoint was VT/VF recurrence and secondary endpoint was death by all cause. Kaplan-Meier estimated the risk of VT/VF recurrence was significantly smaller with EPS-guided amiodarone ($p<0.01$) but not with Holter-guided amiodarone. Multivariate Cox hazard analysis revealed that EPS-guided amiodarone was an independent factor suppressing the recurrence of VT/VF ($p<0.05$, 95% confidence interval=0.15 to 0.96). In the subgroup analysis, EPS-guided amiodarone was effective in patients with relatively well-preserved left ventricular ejection fraction (LVEF ≥ 0.30) but not in patients with lower LVEF (LVEF <0.30).

Conclusion EPS-guided amiodarone was useful for preventing recurrence of VT/VF in patients with a relatively well-preserved LVEF, but not always beneficial in patients with a lower LVEF. (Circ J 2008; 72: 88–93)

Key Words: Amiodarone; Electrophysiologic study; Holter monitoring; Ventricular fibrillation; Ventricular tachycardia

Ventricular tachyarrhythmias are critically important in the prognosis of patients with structural heart diseases. Amiodarone is one of the most advocated antiarrhythmic drugs available for preventing the recurrence of ventricular tachycardia (VT), ventricular fibrillation (VF), thereby reducing total mortality in patients with VT/VF.^{1–4} Although an electrophysiologic study (EPS) and Holter monitoring are performed to evaluate the efficacy of antiarrhythmic drugs, oral amiodarone is often prescribed empirically because the antiarrhythmic effect as guided by EPS or Holter monitoring is controversial.^{5–9} Recent clinical trials have shown that an implantable cardioverter defibrillator (ICD) is clearly superior to amiodarone for preventing sudden arrhythmic death,^{10–13} but cannot prevent the recurrence of VT/VF and sometimes gives an intolerable shock to the patient. Therefore, it is still important to clarify how to optimize amiodarone and/or ICD therapies in patients with sustained VT/VF and structural heart diseases.^{14,15}

On the other hand, patients with a lower left ventricular

ejection fraction (LVEF) derive significantly more benefit from ICD therapy than those with a better preserved LVEF.^{16–18} Moreover, a recent randomized study reported that amiodarone had no favorable effect on survival but that ICD therapy reduced overall mortality by 23% in patients with congestive heart failure and LVEF $<35\%$.¹⁹ Therefore, a cardiac function parameter, such as LVEF, is important in determining the prognosis of patients with sustained VT/VF. The goals of this study were: (1) to evaluate whether or not EPS- or Holter monitoring-guided therapy can stratify the risk of VT/VF recurrence after oral amiodarone, and (2) to investigate the extent to which specific patients subgroups benefit differently from amiodarone therapy.

Methods

Patients

This study retrospectively analyzed 400 patients who had been treated with oral amiodarone at the National Cardiovascular Center (Suita, Japan) from 1990 to 2004. All patients had a history of symptomatic sustained VT/VF because of structural heart diseases. We excluded 212 patients with a LVEF >0.50 , treated with amiodarone for non-sustained VT or atrial arrhythmias, or who had undergone radiofrequency catheter ablation or surgical procedures for VT/VF. Therefore, this study registered 188 patients (mean age, 60 ± 12 years; 149 males), which included 77 patients with previous myocardial infarction, 61 with dilated cardio-

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Table 1 Patients' Characteristics

	Overall	EPS-post amiodarone		EPS (–)
		VT (–)	VT (+)	
<i>n</i>	188	27	62	99
Age (years)	60±12	59±9	58±11	61±14
Sex (male, %)	149 (79)	22 (81)	48 (77)	80 (81)
LVEF (%)	30±12	30±11	34±11	28±12*
Structural heart disease (%)				
Old MI	77 (41)	14 (52)	24 (39)	39 (39)
DCM	61 (33)	7 (26)	18 (29)	36 (36)
HCM	8 (4)	0 (0)	4 (6)	4 (4)
ARVC	16 (9)	1 (4)	6 (10)	9 (9)
Sarcoidosis	11 (6)	2 (7)	6 (10)	3 (3)
Valvular heart disease	12 (6)	1 (4)	3 (5)	8 (8)
Other	3 (1)	2 (7)	1 (1)	0 (0)
Presenting arrhythmias (%)				
Sustained VT	150 (80)	23 (85)	56 (91)	70 (71)
VF	26 (14)	4 (15)	2 (3)	21 (21)
Sustained VT and VF	12 (6)	0 (0)	4 (6)	8 (8)
VF total (%)	38 (20)	4 (15)	6 (9)	29 (29)*
ICD (%)	81 (43)	7 (26)	40 (65)**	34 (34)
Medication (%)				
ACEI	103 (55)	18 (67)	30 (48)	55 (55)
-blocker	102 (55)	12 (44)	34 (55)	56 (57)
Digitalis	60 (32)	9 (33)	13 (21)	38 (38)

EPS, electrophysiological study; VT (–), VT or VF is not induced by EPS; VT (+), VT or VF is induced by EPS; LVEF, left ventricular ejection fraction; MI, myocardial infarction; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; VT, ventricular tachycardia; VF, ventricular fibrillation; ICD, implantable cardioverter defibrillator; ACEI, angiotensin converting enzyme inhibitors.

* $p < 0.05$ vs EPS-VT (+) group; ** $p < 0.05$ vs EPS-VT (–) and EPS (–) group.

myopathy, 16 with arrhythmogenic right ventricular cardiomyopathy, 8 with hypertrophic cardiomyopathy, and 11 with cardiac sarcoidosis. The mean LVEF of these patients was $30 \pm 12\%$ (Table 1).

EPS and Holter Monitoring

After written informed consent was given, EPS was performed in the fasting, nonsedated state before (pre) and 1 month after (post) starting oral amiodarone. All other anti-arrhythmic drugs were discontinued. The protocols of the programmed ventricular stimuli have been described in detail previously.⁴ In brief, up to 3 premature extrastimuli after an 8-beat stimulus drive were delivered from the right ventricular apex and outflow tract using a quadripolar-electrode catheter, and incremental ventricular stimulation with a constant cycle length. The stimulation protocol was terminated when sustained VT or VF was induced. The efficacy of amiodarone was determined by whether or not a run of VT >15 beats could be induced during EPS after starting amiodarone. Thus, we were not concerned about the inducibility of VT/VF before amiodarone therapy.

Twenty-four hours Holter electrocardiogram was recorded on magnetic tape before drug therapy, and repeated 1 month after administration of amiodarone and analyzed by computer to determine the frequency of arrhythmias. The efficacy of amiodarone by Holter recording was assessed by the criteria of the ESVEM trial.²⁰ First, patients with total premature ventricular contractions (PVC) less than 300/day before amiodarone were excluded from the Holter judgment as an “undetermined” group. Therefore, patients with total PVCs more than 300/day before amiodarone and 70% reduction in the PVC count, 80% reduction in the PVC pair count, 90% reduction in the VT count, and absence of any runs of VT >15 beats were defined as “effective”, but patients with no response to these criteria were defined as

Table 2 EPS and Holter Judgments

	EPS post amiodarone		EPS-post (–)
	VT (–)	VT (+)	
<i>EPS pre amiodarone</i>			
VT (–) (n=2)	1	0	1
VT (+) (n=37)	3	16	18
EPS-pre (–) (n=149)	23	46	80
Total (n=188)	27	62	99
<i>Holter criteria</i>			
Effective (n=37)	7	9	21
Ineffective (n=38)	7	10	21
Undetermined (n=113)	13	43	57

EPS-pre (–), EPS before amiodarone is not performed; EPS-post (–), EPS after amiodarone is not performed. Other abbreviations see in Table 1.

“ineffective”.

Follow-up After Amiodarone

Whether or not they had EPS or Holter monitoring, all patients continued treatment with amiodarone, the loading dose of which was 300 or 400 mg/day for 2 weeks followed by a maintenance dose of 150 or 200 mg/day. However, amiodarone was discontinued when critical side effects developed or it was obviously ineffective. All patients were followed up to 36 months and the primary endpoint was recurrence of VT/VF and the secondary endpoint was death from all causes. Implantation of an ICD was recommended in patients who were considered to be “ineffective” with amiodarone or had a history of syncope because of VT/VF.

Statistical Analysis

The continuous variables are expressed as mean ± SD and were compared by an unpaired t-test when appropriate. Cumulative event rates were calculated by the Kaplan-

Fig 1. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) after amiodarone therapy in patients judged by electrophysiological study (EPS) criteria. EPS stratified the risk of VT/VF recurrence after amiodarone. EPS-VT(+), patients with inducible VT/VF by EPS after amiodarone; EPS-VT(-), patients with no inducible VT/VF by EPS after amiodarone; EPS(-), patients without EPS after amiodarone.

Fig 2. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) after amiodarone therapy in patients judged by Holter-monitoring criteria. Holter-monitoring could not stratify the risk of VT/VF recurrence after amiodarone. Effective, patients judged amiodarone effective by Holter; Ineffective, patients judged amiodarone ineffective by Holter; Undetermined, patients excluded from the Holter judgment.

Table 3 Cox Hazard Regression Analysis of VT/VF Recurrence

	OR (95%CI)	p value
Age	1.26 (0.80–1.99)	0.33
Sex (male)	0.93 (0.54–1.60)	0.78
Basal disease (Old MI)	0.75 (0.45–1.25)	0.27
LVEF <30%	1.47 (0.94–2.32)	0.09
EPS post amiodarone		
VT (+)	1.71 (1.07–2.75)	0.02
VT (-)	0.34 (0.15–0.96)	0.04
Holter judgment		
Ineffective	1.47 (0.87–2.50)	0.15
Effective	0.77 (0.42–1.43)	0.42

Abbreviations as in Tables 1,2.

Meier method. The significance of the difference between treatment groups was assessed with the log-rank test. Cox regression analysis was performed on the patients' baseline characteristics to investigate and compare the influence of different variables. Statistical significance was established as $p < 0.05$.

Results

EPS and Holter Monitoring

Table 2 summarizes the results of EPS and Holter monitoring. The EPS before amiodarone was performed in 39 patients, and induced VT/VF in 37 (95%). The EPS after amiodarone was performed in 89 patients, and could not induce VT/VF in 27 (30%) patients (EPS-VT(-) group), but still induced VT/VF in 62 (70%) patients (EPS-VT(+) group). The remaining 99 patients taking amiodarone without judgment by EPS were defined as EPS(-) group.

Holter monitoring before and after amiodarone treatment was recorded in 139 patients; however, 64 patients had less PVCs than the Holter evaluation before amiodarone (300/day). Therefore, the remaining 75 patients were judged as amiodarone effective ($n=37$) or ineffective ($n=38$) by Holter monitoring.

Follow-up

During the follow-up period of 23 ± 13 (range 1–36) months, 82 (44%) patients had recurrence of VT. Moreover, 28 (20%) patients died during follow-up because of heart failure ($n=8$), sudden unexpected death ($n=8$), pneumonia ($n=2$), and unknown causes ($n=10$). Side-effects of amiodarone occurred in 39 (21%) patients, including hypothyroidism ($n=20$), proarrhythmia ($n=5$), pneumonia ($n=11$), leukocytopenia ($n=1$), and liver dysfunction ($n=2$). Amiodarone was discontinued in 13 (8%) patients because of serious side-effects.

Fig 1 illustrates the follow-up results of patients under the EPS criteria. Among those assigned to the EPS-VT(+) group, the rate of VT/VF recurrence was 45.6% and 63.9% at 1 and 3 years, respectively. Conversely, in the EPS-VT(-) group it was 21.3% and 21.3%, and for the EPS(-) group 31.0% and 46.6% at 1 and 3 year's follow-up, respectively. Therefore, the VT/VF recurrence risk after amiodarone was significantly lower in the order of EPS-VT(-), EPS(-), and EPS-VT(+) groups ($p < 0.003$). Table 1 summarizes the clinical characteristics in the 3 groups. Age, sex, basal disease, and medication, except antiarrhythmic drugs, did not differ between them, although LVEF was lower in the EPS(-) group than in the EPS-VT(+) group ($28 \pm 12\%$ vs $34 \pm 11\%$; $p=0.01$), and VF incidence before amiodarone was higher in the EPS(-) group than in the EPS-VT(+) group (29% vs 9%; $p=0.01$). ICDs were consequently implanted in many of the EPS-VT(+) group compared with the EPS-VT(-) and EPS(-) groups (65% vs 26%, 34%, respectively; $p < 0.05$).

Fig 2 illustrates the follow-up results under the Holter criteria. In the patients assigned to the effective group, the VT/VF recurrence rates were 19.1% and 42.8% (1 and 3 years, respectively), whereas in the ineffective group, they were 43.4% and 59.6% (1 and 3 years, respectively) ($p=NS$). Therefore, Holter monitoring cannot stratify the risk of VT/VF recurrence after amiodarone.

Table 3 shows the results of multivariate Cox hazard regression analysis for the recurrence of VT/VF after amiodarone. The clinical factors, age, gender, basal disease

Fig 3. Cumulative risk of recurrent ventricular tachycardia/fibrillation (VT/VF) and total death after amiodarone therapy in different range of left ventricular ejection fraction (LVEF). Electrophysiological study (EPS) judgment could classify the risk of recurrent VT/VF and mortality after amiodarone in patients with LVEF $\geq 30\%$ (A and C, respectively) but not in those with LVEF $< 30\%$ (B and D, respectively). EPS-VT(+), patients with inducible VT/VF by EPS after amiodarone; EPS-VT(-), patients with no inducible VT/VF by EPS after amiodarone; EPS(-), patients without EPS after amiodarone.

(myocardial infarction) and Holter judgments were not related to VT/VF recurrence. The independent clinical factors for VT/VF recurrence were inducibility of VT/VF by EPS after amiodarone (odds ratio (OR) 1.71, 95% confidence interval (CI) 1.07–2.75, $p=0.02$). Lower LVEF ($< 30\%$) increased the risk of VT/VF recurrence but not significantly (OR 1.47, 95% CI 0.94–2.32, $p=0.09$).

EPS-Guided Amiodarone Therapy and LVEF

Because of the possibility of lower LVEF increasing risk of VT/VF recurrence after amiodarone, we evaluated the EPS-guided amiodarone therapy in subgroups. Therefore, among the patients with relatively preserved LVEF ($\geq 30\%$) ($n=94$), there was no VT/VF recurrence in the EPS-VT(-) group, whereas the rates of VT/VF recurrence for the EPS-VT(+) group were 42.1% and 58.5%, and those for the EPS(-) group were 32.3% and 42.7% (at 1 and 3 years, respectively) (Fig 3A). Thus, the risk of VT/VF recurrence was significantly lower in the EPS-VT(-) group compared with the EPS-VT(+) and EPS(-) groups. In contrast, among patients with lower LVEF ($< 30\%$) ($n=91$), the rates of VT/VF recurrence for the EPS-VT(+) group were significantly higher (58.6% and 76.4% at 1 and 3 years, respectively) than those for the EPS-VT(-) (35.7% and 35.7%) and EPS(-) group (30.0% and 51.0%, respectively) ($p < 0.05$), whereas there was no significant difference in the recurrence rate between the EPS-VT(-) and the EPS(-) groups (Fig 3B). Furthermore, in patients with LVEF $\geq 30\%$, no patients died in the EPS-VT(-) group, whereas 3 of 42 patients in the EPS-VT(+) group and 4 of 39 patients in the EPS(-) group died during follow-up (Fig 3C). However, in patients with LVEF $< 30\%$, 2 of 14 patients in the EPS-VT(-), 4 of 20 patients in the EPS-VT(+) and 15 of 55 patients in the EPS(-) group died during follow-up ($p=NS$) (Fig 3D).

Table 4 shows the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for recurrence of VT/VF for Holter, EPS pre-post and EPS-post

Table 4 Predictors of Arrhythmic Events

	SNS	SPC	PPV	NPV	ACC
Holter-judgment ($n=75$)	55	59	58	56	57
EPS pre-post amiodarone ($n=19$)	69	100	100	38	74
EPS post amiodarone ($n=89$)	59	81	88	46	66
LVEF $\geq 30\%$ ($n=55$)	52	100	100	35	62
LVEF $< 30\%$ ($n=34$)	70	64	74	60	68

SNS, sensitivity; SPC, specificity; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy. Other abbreviations as in Table 1.

amiodarone therapy. The EPS judgment showed lower sensitivity but significantly higher specificity for recurrence of VT/VF, especially in patients with LVEF $\geq 30\%$.

ICD and LVEF

We further analyzed the relationship between ICD and LVEF in patients treated with amiodarone. As shown in Fig 4A, the mortality of patients treated with amiodarone plus ICD did not differ between patients with higher ($\geq 30\%$) and lower ($< 30\%$) LVEF. However, among patients with no ICD (amiodarone only) (Fig 4B), patients with LVEF $\geq 30\%$ had a similar mortality to those with ICD, but patients with LVEF $< 30\%$ had a significant worse mortality than the patients with higher LVEF ($p=0.01$). Therefore, patients with moderate to severe LV dysfunction achieved the greatest benefit from ICD therapy.

Discussions

Major Findings

This study retrospectively demonstrated the long-term effect of EPS-guided oral amiodarone therapy in Japanese patients with a history of life-threatening ventricular tachyarrhythmias because of structural heart diseases. EPS-guided amiodarone could reduce the recurrence of VT, especially in patients with relatively preserved ($\geq 30\%$)

Fig 4. Cumulative risk of total death after amiodarone therapy in patients with implantable cardioverter defibrillator (ICD) (ICD(+)) and without ICD (ICD(-)). Higher ($\geq 30\%$) and lower ($< 30\%$) left ventricular (LV) ejection fraction (EF) have similar risk for mortality in ICD(+) patients (A), but higher LVEF has significantly smaller risk of mortality than lower LVEF in ICD(-) patients (B).

LVEF, but was not always beneficial in patients with lower ($< 30\%$) LVEF. Therefore, amiodarone-treated patients with lower LVEF but not an implanted ICD remain at higher risk of sudden death.

EPS or Holter-Guided Amiodarone

Previous studies showed that EP-guided amiodarone therapy was useful for predicting recurrence of VT in patients at high risk for sudden cardiac death.^{5,7,8,21} McGovern et al reported that the sensitivity, specificity and accuracy of EP testing for recurrent VT was 58%, 91% and 67%, respectively.²² Those data coincide with our results showing that EPS-guided therapy has low sensitivity (59%), but high specificity (81%), for recurrence of VT after amiodarone. Moreover, this low sensitivity and high specificity of EP testing is more prominent in patients with LVEF $\geq 30\%$ (52% and 100%, respectively) (Table 4). In this study, there were a small number of patients available for checking inducibility of VT before amiodarone, but the results of EPS-guided amiodarone are similar to those previously reported. Thus, it is not necessary to perform an EPS before starting amiodarone, and patients with LVEF $\geq 30\%$ and non-inducible VT according to the EPS after amiodarone may remain free from recurrence of VT.

The ESVEM study showed that there was no significant difference between EPS and Holter monitoring in the probability of arrhythmic events occurring after antiarrhythmic drugs.²⁰ However, that study mainly examined the effectiveness of class I antiarrhythmic drugs, not amiodarone. The efficacy of amiodarone by Holter monitoring is also controversial. Veltri et al reported that Holter monitoring could predict the long-term efficacy of amiodarone.⁶ Nasir et al showed that amiodarone strongly suppressed PVCs but this suppression did not predict clinical outcome.²³ Our finding that a Holter judgment could not predict the recurrence of VT after amiodarone may have resulted because (1) there was a smaller number of patients undergoing Holter monitoring before and after amiodarone, (2) twenty-four hours recording cannot detect the number of PVCs or VT precisely, and (3) the apparent number of PVCs might have no relation to the trigger of critical VT or VF. In this study EPS was clearly superior to Holter monitoring for evaluating amiodarone efficacy, but EPS is invasive and is not always performed in all patients.

Amiodarone, ICD and LVEF

Zhu et al suggested that EPS testing during amiodarone therapy was useful for predicting arrhythmia recurrence in

patients without new or worsening congestive heart failure.⁷ Other previous reports suggest that patients with lower LVEF ($< 35\%$) have a higher incidence of sudden cardiac death after amiodarone.^{16–18} Those results are consistent with our subgroup analysis showing that EPS-guided amiodarone therapy is beneficial for patients with LVEF $\geq 30\%$ but not $< 30\%$. Therefore, it is suggested that ICD is indicated in patients with lower LVEF ($\leq 30–35\%$) and a history of syncope or sustained VT/VF.^{17,24,25} On the other hand, patients with a relatively preserved LVEF ($\geq 35\%$) do not always have better survival by ICD compared with amiodarone.¹⁶

In this study, EPS-guided amiodarone responders with a LVEF $\geq 30\%$ were considered to be lower risk for sudden cardiac death, whereas patients judged as amiodarone non-responders or with LVEF $< 30\%$ remain high risk for sudden death. Although our data could not compare between amiodarone and ICD therapy in high-risk patients, amiodarone-treated patients with lower LVEF, but not an implanted ICD, remain at higher risk of sudden death (Fig 4B) and should be considered for additional ICD therapy, as previously reported.²⁴

In patients with congestive heart failure and LVEF $< 35\%$, a recent randomized study reported that amiodarone has no favorable effect on survival compared with placebo, but that ICD therapy reduced overall mortality by 23%.¹⁹ Although ICD reduces mortality compared with antiarrhythmic drugs, it is estimated that up to 50% of patients with an ICD ultimately need antiarrhythmic drug therapy to suppress frequent episodes of VT or supraventricular tachyarrhythmias, and that amiodarone is the most commonly used drug for this purpose in Japanese patients.¹⁵ Recently, Connolly et al reported that amiodarone plus β -blocker was effective for preventing ICD shocks, but increased the risk of drug-related adverse effect.²⁶ Therefore, further studies in the Japanese patient population are necessary to evaluate whether or not amiodarone can improve a patient's clinical outcome by reducing the amount of ICD shocks.¹⁴

Study Limitations

First, the study was not a prospective evaluation of EPS- or Holter-guided amiodarone treatment, so the direct efficacy of EPS or Holter-guided amiodarone in preventing the recurrence of VT/VF was not demonstrated; rather, an excellent prognosis for patients treated with EPS-guided amiodarone, especially in patients with a well-preserved LVEF, was demonstrated. Second, this study compared follow-up results between patients judged as amiodarone responder or non-responder by EPS, but did not compare

amiodarone responders with control patients. Therefore, it might overestimate the effectiveness of EPS-guided amiodarone therapy for suppression of recurrent VT/VF. Third, this study contained a small number of patients, and a multicenter trial with a large number of patients will be necessary to demonstrate the effect of amiodarone and ICD therapy more accurately in Japanese patients!^{14,15} Fourth, this study focused on the risk of recurrent (secondary) VT/VF, not on primary prevention. It is still controversial whether amiodarone and/or ICD are indicated in patients with non-sustained VT and lower LVEF for primary prevention of sudden death.

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