Role of Electrophysiologic Study (EPS)-Guided Preventive Therapy for the Management of Ventricular Tachyarrhythmias in Patients With Heart Failure

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Background Ventricular tachyarrhythmias (VT/VF) are 1 of the most important factors determining the prognosis of patients with heart failure (HF). Although priority is given to implantable cardioverter defibrillator (ICD) therapy for the prevention of sudden cardiac death, electrophysiologic-study (EPS)-guided preventive therapy could be important for reducing the number of cardiac events.

Methods and Results Of 864 patients with a history of HF, an EPS was performed in 168 and 121 had inducible VT/VF. Under the basic therapy of an ICD, additional catheter ablation was attempted for 95 of 124 monomorphic VT foci in 74 patients, and 78 of the VT were successfully ablated. The prognoses were compared among 5 patient groups with different results for the EPS and catheter ablation: (1) success group (n=43), (2) failure group (n=15), (3) not attempted group (n=16), (4) VF group (n=47), and (5) no inducible VT/VF group. During a follow-up period of 31±22 months, the incidence of VT/VF was lower in the success and no inducible VT/VF groups than in the other groups (p=0.0018), although a significant difference was not observed for the total deaths.

Conclusion EPS-guided preventive therapy using an ICD and catheter ablation can be useful, at least for the reduction of arrhythmic events in patients with HF. (Circ J 2008; 72: 268–273)

Key Words: Catheter ablation; Electrophysiologic study; Heart failure; Implantable cardioverter defibrillator; Ventricular tachycardia

The incidence of death in patients with heart failure (HF) is considerably high and approximately one-third of the deaths are reported to be the result of serious arrhythmic events.1–5 Therefore, the prevention of sudden death is an important issue in the management of patients with HF. Although priority is given to implantable cardioverter defibrillator (ICD) therapy6–8 in practice it is impossible to assign all HF patients to this.9 Additionally, defibrillation shocks are quite uncomfortable for patients, so preventive therapy is necessary even for patients who undergo ICD implantation.10–13 In the present study, we evaluated the efficacy of preventive therapy using catheter ablation during the electrophysiologic study (EPS) in patients with HF and inducible ventricular tachyarrhythmias (VT/VF) in order to clarify the role of EPS-guided preventive therapy as secondary and primary prevention of arrhythmic events or total death in this patient group.

Subjects Of 864 patients with a history of hospitalization because of HF (>New York Heart Association (NYHA) II), an EPS was performed in 168 because of spontaneous VT/VF episodes (n=67) or an episode of nonsustained VT (NSVT >5 beats) during long-term (>24h) ECG monitoring (n=101).14 Of the 101 patients with NSVT, VT/VF was inducible by programmed electrical stimulation in 54. The clinical characteristics and long-term prognoses were evaluated in 168 patients who underwent an EPS. The mean age was 63±9 years, and 61 patients were women and 107 were men. The basic structural heart disease was ischemic in 85, dilated or hypertrophic cardiomyopathy in 47, valvular in 31, and other heart diseases in 5 patients. All patients underwent echocardiography and cardiac catheterization, and the diagnosis of structural heart disease was based on the findings of coronary angiography and left ventriculography in all cases, plus left ventricular (LV) myocardial biopsy in selected cases (n=44). The clinical grade of HF (NYHA grade) was determined while stable during long-term follow-up. The basic clinical characteristics are summarized in Table 1. All studies were performed after obtaining written informed consent and the permission of the Clinical Studies and Ethics Committee of Kitasato University Hospital.
Induction Protocol All antiarrhythmic agents, except for amiodarone, were discontinued for 5 half-lives before the study. In the patients with pre-administration of amiodarone (n=6/67 of the patients with previous spontaneous VT/VF episodes), ICD implantation was performed prior to the EPS, which was then performed after discontinuing the amiodarone for 4–8 weeks. The induction protocol for VT/VF consisted of 1–3 extrastimuli with 2 basic drive cycle lengths (CL: 400 and 600 ms) and rapid ventricular pacing at fixed CLs delivered from 2 right ventricular sites. When VT/VF could not be induced by electrical stimuli alone, isoproterenol was infused intravenously and the entire stimulation protocol was repeated. To eliminate the induction of nonspecific arrhythmias, coupling intervals of the extrastimuli <180 ms were not delivered, even when they could capture the ventricle.

Catheter Ablation When monomorphic VT was induced in the EPS, catheter ablation was attempted for all foci in principle, including those with a nonclinical QRS morphology. In selected patients, catheter ablation was not attempted in compliance with the patient's choice or condition. Standard markers were used for the ablation of VT foci: (1) earliest activation site during VT, (2) pace-mapping site that exhibited the best match of the QRS morphologies on the 12-lead ECG (pace-mapping), (3) mid-diastolic potential satisfying the criteria of a central common pathway of a reentrant circuit, or (4) a canal between scar regions based on voltage mapping using an electro-anatomical mapping system. In the VT-oriented evaluations, catheter ablation was considered effective when all VTs were successfully ablated.

Basic Treatment Strategy for the Arrhythmias All patients with inducible VT/VF were assigned to ICD therapy in principle. Catheter ablation for monomorphic VT was attempted in each case as described above. An EPS-guided evaluation of the pharmacological therapy was performed in selected cases, but no antiarrhythmic agents were used during at least the observation period of this study. In cases of VT/VF occurrence during the observation period, several antiarrhythmic agents were later started, but episodes of arrhythmia after the addition of these agents were not assessed in this study. Patients without any inducible VT/VF during the EPS were followed up without any antiarrhythmic therapy, except for the basic therapies for HF, including diuretics, β-blockers or angiotensin-converting enzyme inhibitors (ACEIs) etc, when the patients did not have spontaneous VT/VF episodes.

Clinical Follow-up In the patient-oriented evaluations the patients were divided into 5 groups based on the intention and results of VT/VF induction and then catheter ablation: (1) success group, (2) failure group, (3) not attempted group, (4) VF group, and (5) no inducible VT/VF group. The populations and results of catheter ablation of these groups are summarized in Table 2. The clinical characteristics and the incidences of arrhythmic events or death were compared among the 5 groups. In this study, an arrhythmic event was defined as electrocardiographically documented and hemodynamically unstable VT/VF, including records from the ICD or sudden death in patients without ICD therapy. Total death was defined as death from any cause, including arrhythmic episodes or worsening of HF.

### Table 1 Clinical Characteristics of the Patients

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Spontaneous VT/VF</th>
<th>Inducible VT/VF</th>
<th>No inducible VT/VF</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>168</td>
<td>67</td>
<td>54</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63±9</td>
<td>63±9</td>
<td>65±6</td>
<td>61±10</td>
<td>0.061</td>
</tr>
<tr>
<td>Gender (male %)</td>
<td>63.7</td>
<td>64.2</td>
<td>62.9</td>
<td>63.8</td>
<td>0.891</td>
</tr>
<tr>
<td>Basic heart disease (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>85</td>
<td>30</td>
<td>31</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>CM</td>
<td>47</td>
<td>18</td>
<td>12</td>
<td>17</td>
<td>0.273</td>
</tr>
<tr>
<td>VHD</td>
<td>31</td>
<td>17</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Induced arrhythmia (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monomorphic VT</td>
<td>78</td>
<td>51</td>
<td>27</td>
<td>–</td>
<td>0.003*</td>
</tr>
<tr>
<td>VF</td>
<td>43</td>
<td>16</td>
<td>27</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37±9</td>
<td>36±8**</td>
<td>34±6**</td>
<td>39±7</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

* p<0.05 vs no inducible VT/VF group.

VT/VF, ventricular tachyarrhythmias; IHD, ischemic heart disease; CM, cardiomyopathy; VHD, valvular heart disease; LVEF, left ventricular ejection fraction.

### Table 2 Intention and Result in Catheter Ablation for VT/VF

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Spontaneous VT/VF</th>
<th>Inducible VT/VF</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>121</td>
<td>67</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>VT morphologies</td>
<td>1.7±0.8</td>
<td>1.8±0.8</td>
<td>1.4±0.6</td>
<td>0.0297*</td>
</tr>
<tr>
<td>Result of ablation (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>43</td>
<td>24</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>15</td>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Not attempted</td>
<td>20</td>
<td>16</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>VF</td>
<td>43</td>
<td>16</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

Success, all VTs ablated; Failure, more than 1 VT remained. Other abbreviation see in Table 1.
Statistical Analysis

Data are presented as the mean ± standard deviation. The statistical analyses were performed using the Wilcoxon test and Kaplan-Meier survival curves, or the t-test, using JMP statistical software (SAS Institute Inc, Cary, NC, USA). A p-value <0.05 was considered significant.

Results

Patient Population and Clinical Characteristics

The number of patients with a history of spontaneous VT/VF was 67 (7.8%) of the 864 patients who were hospitalized because of HF. The number of episodes of NSVT (>5 beats) on the Holter ECG recording was 101 in the remaining 797 patients (12.7%) and that of inducible VT/VF during the EPS was 54/101 (53.5%). In total, the population of patients at higher or lower risk for an arrhythmic event was 121 (67+54) plus 47 in the EPS-guided risk stratification of 168 patients with spontaneous VT/VF or NSVT. These 168 patients were divided into 5 groups according to the intention and results of VT/VF induction and catheter ablation: 43 patients were placed in the success group, 15 in the failure group, 20 in the not attempted group, 43 in the VF group and the remaining 47 in the no inducible VT/VF group. There was no significant difference among the 5 groups in age, gender or basic heart disease. However, the LV ejection fraction (LVEF) was significantly higher in the no inducible VT/VF group than in the other groups (Table 3). There was no difference among the groups in the usage of ß-blockers and/or angiotensin-receptor blocker/ACEI during the follow-up period (Table 3). The clinical grade of HF (NYHA grade) shifted in most of the patients to grade II or III during the long-term observation, and there was no significant difference among the 5 groups (Table 3).

Of the 67 patients with a history of spontaneous VT/VF (ie, patients with secondary prevention of VT/VF), 24 were placed in the success group, 11 in the failure group, 20 in the not attempted group, 16 in the VF group and the remaining 17 in the no inducible VT/VF group. There was no significant difference among the 5 groups in age, gender or basic heart disease. However, the LV ejection fraction (LVEF) was significantly higher in the no inducible VT/VF group than in the other groups (Table 3). There was no difference among the groups in the usage of ß-blockers and/or angiotensin-receptor blocker/ACEI during the follow-up period (Table 3). The clinical grade of HF (NYHA grade) shifted in most of the patients to grade II or III during the long-term observation, and there was no significant difference among the 5 groups (Table 3).

Of the 101 patients without a history of spontaneous VT/VF, 54 had inducible VT/VF during the EPS, but the remaining 47 patients did not have a history of spontaneous VT/VF.
not and they were placed in the no inducible VT/VF group. Of the 54 patients with inducible VT/VF (ie, those with primary prevention of VT/VF), 19 were placed in the success group, 4 in the failure group, 4 in the not attempted group, and 27 in the VF group (Table 2). The number of VT morphologies was higher in the patients with spontaneous VT/VF than in the patients without spontaneous VT/VF. The population of patients with VF was greater among the patients without spontaneous VT/VF than in those with spontaneous VT/VF (Table 2).

**Patients' Prognoses**

Fig 1 shows the event-free survival curves for an arrhythmic event or total death in the 5 groups during the follow-up period of 31±22 months. VT/VF occurred in 7/43 in the success group, 7/16 in the failure group, 5/11 in the not attempted group, and 5/47 in the no inducible VT/VF group. The incidence of an arrhythmic event was significantly lower in the success and no inducible VT/VF groups than in the other 3 groups (p=0.0018). Sudden death because of severe cardiac arrhythmia was prevented by the action of the ICD in 4 patients in the success group, 2 in the failure group, 2 in the not attempted group, and 2 in the VF group (Table 3). Although the incidence of total death seemed to be lower in the success, VF and no inducible VT/VF groups than in the others during the earlier phase of the observation, the difference was not significant (Fig 1).

Figs 2 and 3 show similar event-free survival curves for an arrhythmic event or total death in the 5 groups after subdivision into secondary and primary prevention of VT/VF. Fig 2 shows the event-free survival curves for patients with a history of spontaneous VT/VF (n=67). Because there was no patient without inducible VT/VF during the EPS, the curves for the no inducible VT/VF group are not shown. During observation of the secondary prevention of VT/VF, an arrhythmic event occurred in 5/24 of the success group, 7/16 of the failure group, 5/11 of the not attempted group, and 4/27 in the VF group. Similar to the total population, the incidence of arrhythmic events was significantly lower in the success group than in the other 3 groups (p=0.0018). Sudden death because of severe cardiac arrhythmia was prevented by the action of the ICD in 4 patients in the success group, 2 in the failure group, 2 in the not attempted group, and 2 in the VF group (Table 3). Although the incidence of total death seemed to be lower in the success, VF and no inducible VT/VF groups than in the others during
events was significantly lower in the success and no inducible VT/VF groups than in the other 3 groups (p=0.0309). The difference in total deaths did not reach statistical significance, although it seemed to be lower in the success, VF and no inducible VT/VF groups during the earlier phase of the observation.

Discussion

Incidence of HF Patients at Risk for Arrhythmic Events

Although EPS-guided risk stratification might be a reliable method of selecting the patients at risk for future arrhythmic events out of a population with LV dysfunction in practice it is impossible for all patients to undergo an EPS. In patients with a history of VT/VF and LV dysfunction, ICD implantation is given priority even without an EPS. However, in patients without a previous history of VT/VF, some clinically useful parameters for noninvasive evaluation are necessary in order to assign appropriate patients to an invasive test such as an EPS. It has been reported that a history of unexplained syncope, recording of NSVT, low LVEF, abnormal ventricular late potentials, abnormal T-wave alternans etc might be useful indices of future cardiac events. In the present study, Holter-ECG recording was routinely performed in all patients and the recording of NSVT (>5 beats) was used as an index to assign the patient to EPS-guided risk stratification. Of 864 patients with a history of HF (67 (7.8%) had a previous history of spontaneous VT/VF, 101 (12.7%) of the remaining 797 patients had NSVT (>5 beats), and VT/VF was induced in 54/101 (53.5%) patients. In total, 14.0% (67/4864) of the patients were evaluated as being at risk for an arrhythmic event, and that population was considered to be quite high. When comparing the 5 groups with different results for VT/VF induction or catheter ablation during the EPS, the LVEF was higher in the no inducible VT/VF group than in the other 4 groups, indicating that low LV function might be another important index of the risk for ventricular arrhythmia, whereas in the present study the clinical grade of HF (NYHA grade) did not show significant difference. Other noninvasive parameters, such as ventricular late potentials or T-wave alternans, were not used for risk stratification simply because they were not routinely performed in all patients. However, if other patients with abnormal findings for those additional evaluations had been included, the population of patients at risk would have become larger.

Usefulness of EPS-Guided Risk Stratification and Preventive Therapy With Catheter Ablation

Because basic structural heart disease can progress in patients with HF, arrhythmogenicity is modified over time, resulting in a reduction in the long-term success rate of preventive therapy for VT/VF, even when it is initially effective. Furthermore, the meaning of prevention of inducible VT/VF during the EPS only (ie, primary prevention of VT/VF) is unclear, especially in patients with considerable LV dysfunction? In the present study, the incidence of arrhythmic events was lower in patients with a successful result for catheter ablation of induced monomorphic VT than in patients with an unsuccessful result or no attempt at ablation, indicating that EPS-guided preventive therapy with catheter ablation could reduce arrhythmic events in patients with HF, both for secondary and primary prevention of arrhythmic events. In this study the incidence of arrhythmic events was also lower in patients without inducible VT/VF during the EPS than in the groups of patients with inducible VT/VF (ie, the failure, not attempted or VF groups). This result indicates that EPS-guided risk stratification using inducibility of VT/VF as an index for the risk of future arrhythmic event could be useful in the management of patients with HF. Because there was no significant difference between the success and no inducible VT/VF groups in the incidence of arrhythmic events, we consider that catheter ablation could reduce arrhythmic events in high-risk patients to the same level as that for patients with a lower risk of an event. Although ICD therapy was instituted for most of the present patients at risk for VT/VF, these results indicate that EPS-guided preventive therapy could reduce the chance of defibrillation shocks given by the ICD. The ability of EPS-guided catheter ablation to reduce monomorphic VT has already been documented for secondary prevention, but the present results indicate that the reduction in episodes of VT as a result of catheter ablation can also be expected for primary prevention. Accordingly, catheter ablation of monomorphic VT is recommended if VT can be induced in the EPS.

On the other hand, we could not document any benefit of EPS-guided preventive therapy on total deaths, which might be the result of ICD action because most of the patients who were saved from sudden death because of an arrhythmic event had undergone ICD implantation. However, this result does indicate that EPS-guided therapy reduced the total deaths in the patient population with a higher risk for an arrhythmic event to a similar level as that in the patient population with lower risk, so EPS-guided risk stratification might still be useful for selecting the patients at high risk of sudden death. Another important reason might be death because of HF. Because neither ICD implantation nor catheter ablation is a direct therapy for HF, the progression of the basic heart disease is unaffected by these therapies. Because there were deaths in the patient group with lower risk for an arrhythmic event (ie, the no inducible VT/VF group), we consider that death from HF can not be avoided in patients with severe HF. As a result, the benefit of EPS-guided preventive therapy on overall mortality is unclear, but it should reduce the incidence of uncomfortable shocks caused by the ICD.

Study Limitations

First, both the number of patients and the follow-up period were limited. Second, the types of basic structural heart disease varied within the patient population, which may have affected the results. However, we could document a benefit of EPS-guided preventive therapy in the population including ischemic and non-ischemic heart diseases at least. Third, because we could not address the prognoses of patients without NSVT in this observation, the role of performing an EPS in that cohort remains unclear. Finally, because this study was retrospective, the real meaning of preventive therapy for VT/VF is unclear. Although a prospective study for this type of life-threatening arrhythmia would be difficult in practice, our findings should be reevaluated in the future in a larger number of patients who are undergoing ICD implantation and EPS-guided evaluation.

Conclusion

EPS-guided risk stratification indicated a considerably high incidence of patients at risk for VT/VF in a population of patients with HF. EPS-guided catheter ablation reduced
the number of VT/VF episodes in patients with inducible VT during the EPS, so EPS-guided preventive therapy may be useful for the reduction of arrhythmic events in patients with HF.

References