Clinical Usefulness of Electrophysiologic Study (EPS)-Guided Risk Stratification for Life-Threatening Arrhythmia in Patients With Heart Failure

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SUMMARY

Background: Ventricular tachyarrhythmia is one of the most important factors determining the prognosis of patients with heart failure and sudden death can be observed even during stable therapy controlling clinical heart failure. In this study, the usefulness of electrophysiologic study (EPS) for the prediction of a future arrhythmic event was evaluated in patients with heart failure.

Methods and Results: The patient population consisted of 474 patients with a history of clinical heart failure but without an episode of spontaneous sustained ventricular tachycardia or fibrillation (VT/VF). A Holter ECG was performed in all patients, and 177 of the 474 patients underwent EPS because of a recording of nonsustained VT (NSVT, > 5 beats). When sustained VT/VF was inducible in EPS, the patient was assigned to implantation of a defibrillation device. The patients were divided into 3 groups, ie, 1) no NSVT (n = 297), 2) NSVT + no inducible VT/VF (n = 134), and 3) NSVT + inducible VT/VF (n = 43), and were followed-up for > 12 months. All patients were followed-up under standard therapy for heart failure. There were no significant differences in basic clinical characteristics and therapies among the 3 groups. During the follow-up period of 32 ± 18 months, 56/474 patients suffered a VT/VF episode, ie, 21/297 in no NSVT, 14/134 in NSVT + no inducible VT/VF, and 21/43 in NSVT + inducible VT/VF patients (P = 0.032). All patients were rescued from sudden death among patients with an implanted defibrillator, but 11 patients without a defibrillator died.

Conclusion: In patients with heart failure, future arrhythmic events could be predicted by EPS and Holter ECG. EPS-guided risk stratification seems to be useful in managing patients with heart failure. (Int Heart J 2007; 48: 155-163)

Key words: Ventricular tachyarrhythmia, Ventricular fibrillation, Heart failure, Implantable cardioverter defibrillator, Electrophysiologic study

IN reports regarding clinical mega-studies concerning heart failure, relatively
poor prognoses have been reported regardless of the additional therapies with beta-blockers or angiotensin converting enzyme inhibitors. Importantly, about 1/3 of total deaths was due to a life-threatening arrhythmic event, so that the management of critical ventricular arrhythmia is an important issue in patients with heart failure. Recent studies have revealed that usage of an implantable cardioverter defibrillator (ICD) would be superior to any other preventive therapies, including amiodarone, especially in patients with previous history of spontaneous ventricular tachyarrhythmias, ie, secondary prevention, but ICD cannot be assigned to all patients with heart failure mainly because of its cost-effectiveness. Therefore, practical risk-stratification should be conducted for clinical management of patients with heart failure, especially in the primary prevention of sudden cardiac death. In the present study, an induction study of ventricular tachycardia or fibrillation (VT/VF) by programmed electrical stimulation was performed in patients with heart failure and their prognoses were evaluated to clarify the usefulness of electrophysiologic study (EPS)-guided risk stratification in primary prevention of sudden cardiac death in patients with heart failure.

**METHODS**

**Subjects:** The study population consisted of 474 consecutive patients (mean age, 57 ± 16 years old, 114 females and 360 males) with a history of clinical heart failure (> NYHA III-IV) who required hospital admission. Patients with a history of spontaneous VT/VF were excluded. The basic structural heart disease was ischemic heart disease in 226, dilated or hypertrophic cardiomyopathy in 121, valvular heart disease in 60, and another heart disease in 65. All diagnoses of structural heart disease were based on the cardiac catheterization and echocardiogram findings.

**Holter ECG recording:** Twenty-four hour \(n = 86\) or 48-hour \(n = 388\) Holter ECG recording was performed in all patients (HR-8500, Marquette Electronics, Miami, FL, USA) in a stable condition during chronic medication including beta-blockers or renin-angiotensin system inhibitors to avoid the influence of acute change in ventricular function in the acute phase of heart failure. When nonsustained VT (NSVT, > 5 beats) was recorded in the Holter ECG, the patients were assigned to the VT/VF induction study in EPS. The patients without NSVT recording were followed-up under standard therapies for heart failure.

**Electrophysiologic study (EPS):** *Induction protocol.* The EPS was performed after obtaining written informed consent. All antiarrhythmic agents were discontinued for 5 half-lives before the study. The induction protocol for VT/VF employed 1 to 3 extrastimuli with 2 basic drive cycle lengths (400 and 600 ms) and rapid ventricular pacing at fixed cycle lengths delivered at 2 right ventricular
sites.\textsuperscript{12-15} When VT/VF could not be induced by the electrical stimuli alone, isoproterenol was infused intravenously and the whole stimulation protocol was repeated. To eliminate the induction of nonspecific arrhythmias, coupling intervals of extrastimuli < 180 ms were not delivered even when they could capture the ventricle.\textsuperscript{14}

\textbf{Antiarrhythmic therapy.} If VT/VF could not be induced by the entire induction protocol, the patients were basically followed-up under standard therapies for heart failure without antiarrhythmic therapy. Amiodarone (100-200 mg/day) could be added later when frequent NSVT or premature ventricular contractions were observed during the follow-up treatment,\textsuperscript{14,16} however, this was performed after the observations for this study. If VT/VF could be induced in EPS, the patients were, in principle, assigned to ICD implantation. Catheter ablation was attempted for hemodynamically stable monomorphic VT.\textsuperscript{17} Standard endocardial mapping, pace-mapping, and/or substrate mapping techniques were used to make a decision concerning ablation sites.\textsuperscript{14} Amiodarone administration (100-200 mg/day) was permitted due to episodes of spontaneous VT/VF during the follow-up period, however, not until the observations for this study had been completed.

\textbf{Clinical follow-up.} The patients were divided into 3 groups on the basis of the results of Holter ECG and EPS-guided evaluation, ie, 1) patients without NSVT, 2) patients with NSVT and no inducible VT/VF in EPS, and 3) patients with NSVT and inducible VT/VF in EPS. The patients were followed-up under

\begin{table}
\centering
\caption{Clinical Characteristics of the Patients and Therapies}
\begin{tabular}{lcccc}
\hline
 & Total & NSVT (-) & NSVT (+) & NSVT (+) Inducible VT/VF (+) & \textit{P} \\
\hline
Number (cases) & 474 & 297 & 134 & 43 & \\
Age (years) & 57 ± 16 & 57 ± 17 & 56 ± 20 & 58 ± 14 & 0.834 \\
Gender (male\%) & 76\% & 73\% & 77\% & 78\% & 0.701 \\
Basic heart disease (cases) & & & & & \\
IHD & 226 & 141 & 64 & 21 & \\
CM & 121 & 77 & 33 & 11 & 0.224 \\
Other & 125 & 79 & 37 & 9 & \\
LVEF (\%) & 44 ± 6 & 47 ± 6 & 42 ± 4 & 41 ± 5 & 0.042* \\
Medication (case\%) & & & & & \\
Amiodarone & 6.9 & 0 & 8.2 & 51.2 & 0.0012* \\
Beta-blockers & 85.7 & 85.5 & 82.8 & 76.7 & 0.602 \\
ARB/ACEI & 76.2 & 74.7 & 76.9 & 83.7 & 0.324 \\
Catheter ablation (cases) & 26 & 0 & 0 & 26 & \\
ICD (case) & 40 & 0 & 0 & 40 & \\
\hline
\end{tabular}
\end{table}

NSVT indicates nonsustained VT; VT/VF, ventricular tachycardia or fibrillation; IHD, ischemic heart disease; CM, cardiomyopathy; ARB/ACEI, angiotensin II receptor blockers or angiotensin converting enzyme inhibitor; and ICD, implantable cardioverter defibrillator. * indicates statistical significance.
stable treatment for at least 12 months and the prognoses, ie, arrhythmic events and total death, were compared among the groups. In cases with sudden cardiac death in patients without ICD implantation, the episodes were counted as arrhythmic events in this study.

**Statistical analysis:** Values are presented as the mean ± standard deviation. Statistical analysis was performed by the Wilcoxon test for the Kaplan-Meier survival curve or t-test using JMP statistical software (SAS Institute Inc., Cary, USA). A $P < 0.05$ was considered significant.

**RESULTS**

The Table summarizes the characteristics of the study population. Out of 474 patients, NSVT (> 5 beats) was observed in Holter-ECG in 177 patients and they were assigned to EPS-guided evaluation. Out of the 177 patients, VF was induced in 16, monomorphic VTs were induced in 27, and no VT/VF was induced in the remaining 134 patients. Catheter ablation was attempted for 54 foci in 26 patients, and 33 foci (61%) were successfully ablated at least in the evaluation in the same EPS session. All patients were followed-up under stable treatment for at

![Arrhythmic events](image)

**Figure 1.** Arrhythmic events during the follow-up period. The incidence of spontaneous VT/VF was higher in patients with NSVT and inducible VT/VF in EPS than in the other patient groups ($P = 0.032$). See text for details.
least > 12 months, and the mean follow-up period was 32 ± 18 months. Amiodarone was additionally prescribed later in 11 of 134 patients with NSVT and no inducible VT/VF, and in 22 of 43 patients with NSVT and inducible VT/VF. Administration was after the observations for this study had been completed.

Figure 1 shows the arrhythmic events, ie, VT/VF, during the follow-up period of 32 ± 18 months. Out of 474 patients, 56 patients suffered VT/VF episodes; 21 of 297 patients without NSVT (7.1%), 14 of 134 patients with NSVT and no inducible VT/VF (10.4%), and 21 of 43 patients with NSVT and inducible VT/VF (48.8%). The incidence of arrhythmic events was significantly higher in patients with NSVT and inducible VT/VF than the other 2 groups (P = 0.032). All patients with ICD implantation were rescued from sudden death, but 11 without ICD implantation died; 7 without NSVT, and 4 NSVT and no inducible VT.

Figure 2 shows the total death events during the same follow-up period of 32 ± 18 months. Out of 474 patients, 67 patients died during the follow-up period; 41 of 297 patients without NSVT (13.8%), 20 of 134 patients with NSVT and no inducible VT/VF (14.9%), and 6 of 43 patients with NSVT and inducible VT/VF (13.9%). In contrast to arrhythmic events, the incidence of total death events did not differ among the 3 groups. As described above, 7 of 41 (17.1%) deaths in

![Total death](image)

**Figure 2.** Total deaths during the follow-up period.
In contrast to arrhythmic events, there was no difference in total deaths among the 3 groups. See text for details.
patients without NSVT and 4 of 20 (20.0%) deaths in patients with NSVT and no inducible VT were sudden cardiac death, and the difference was not significant.

The Table also summarizes a comparison of the basic characteristics and therapies among the 3 groups. There were no differences in age, gender, or basic therapies for heart failure including beta-blockers or renin-angiotensin system inhibitors, however, left ventricular ejection fraction was lower in the 2 patient groups with NSVT than in the group without NSVT.

DISCUSSION

Clinical usefulness of EPS-guided risk-stratification in primary prevention: Although an ICD therapy is the most powerful therapy for prevention of sudden cardiac death,6-10) it is practically impossible to assign all heart failure patients to ICD therapy, especially for primary prevention, or in other words, for the patients without previous spontaneous episodes of VT/VF.3,5,8) In the present study, we focused on the primary prevention of sudden cardiac death in patients with a history of heart failure, and risk stratification was performed based on the findings in Holter-ECG and VT/VF inducibility in EPS. It was found that a fatal arrhythmic event was more frequent in patients with NSVT in Holter-ECG and inducible VT/VF in EPS than in the other groups of patients.18) Therefore, the combination of Holter-ECG and EPS-guided risk stratification seemed to be a simple and useful way to detect patients at high-risk for sudden cardiac death. In contrast, this risk stratification could not detect high-risk patients with respect to total death. Because the incidence of sudden death was only 11 of 61 patients without ICD implantation, the main cause of total death depended on the aggravation of heart failure itself.6,8) This result is concordant with the results in early reports concerning the effect of ICD on an improved prognosis in patients with LV dysfunction,9,10) which indicated a significant decrease in arrhythmic death but no change in total death in long-term observation. Most likely, ICD therapy could only change the mode of death from arrhythmia to heart failure in some patients. However, the result also indicates that sudden death could be prevented by ICD implantation because all patients with ICD therapy were rescued from sudden death, even those who suffered serious ventricular tachyarrhythmic events. However, it is unclear whether the incidence of total death could be reduced by applying ICD to a larger population including lower-risk patients.

The role of preventive therapy in this observation is unclear. Although 61% of the foci of monomorphic VTs were successfully ablated in the first EPS session, 21 of 43 patients with inducible VT/VF suffered VT/VF recurrence during the follow-up period. This may indicate the recurrence or aggravation of arrhythmogenic substrate along with the progression of heart failure;8,19,20) but there were
no signs of worsening of heart failure in these patients. Although amiodarone may also affect the clinical outcome,\textsuperscript{21,22} it was not prescribed in these patients, at least not during the observation period of this study.

**Risk stratification with noninvasive clinical testing:** Several clinical indices for sudden death in high-risk patients have been reported, such as ventricular late potential in signal averaged ECG, T wave alternans, decreased heart rate variability, and decreased baroreceptor sensitivity.\textsuperscript{23-25} We cannot discuss these points here because routine evaluation was not performed in the entire patient population in this study. However, because the left ventricular ejection fraction was significantly lower in patient groups with NSVT than in those without NSVT, a simple index of left ventricular contraction disturbance might be correlated with the arrhythmogenicity of ventricular muscle.\textsuperscript{5,18} Additionally, the plasma level of brain natriuretic protein (BNP) may become another index for arrhythmogenicity. Because BNP reflects rather recent ventricular wall tension, the BNP level in the acute phase of heart failure might not reflect long-term prognosis, however, the relationship between prognosis and level of BNP in a stable condition should be evaluated in a future study. Although EPS is reliable, at least for the detection of patients at high risk for a future arrhythmic event,\textsuperscript{26-28} practically, it is difficult to assign all heart failure patients to EPS. In this study, high-risk patients were screened out using Holter-ECG by setting the criteria for EPS assignment as the presence of NSVT > 5 beats. Although there is no evidence to support choosing > 5 beats as a border, the incidence became too high when the border was set at \( \geq 3 \) beats, ie, 231 of 474 patients. However, in accordance with the results obtained in this study, NSVT \( \leq 5 \) beats seemed to indicate a low-risk patient, at least with respect to our observations.

**Limitations:** This study has several limitations. First, because the study was designed retrospectively, catheter ablation was performed in most of the patients with monomorphic VT, and the true natural course of the prognosis was unclear. Second, the result was not compared with the other methods for risk stratification. Finally, because the number of patients was limited, the importance of various clinical parameters for VT/VF recurrence was unclear. These points should be re-evaluated and determined in future studies.

**Conclusions:** In risk-stratification for primary prevention of sudden cardiac death in patients with heart failure, the simple combination of Holter-ECG and EPS-guided evaluation was able to detect high-risk patients and these patients could be rescued from sudden death during follow-up by applying ICD implantation. EPS-guided risk stratification seemed to be reliable and became more feasible by combining with noninvasive evaluation of ventricular arrhythmia.
REFERENCES


