Evaluation of Signal-Averaged Electrocardiography for Clinical Diagnosis in Arrhythmogenic Right Ventricular Dysplasia

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SUMMARY

Arrhythmogenic right ventricular dysplasia (ARVD) is a heart muscle disorder of unknown etiology that is characterized pathologically by fibrofatty replacement of the right ventricular myocardium. We investigated the relationship between the electrocardiogram (ECG) appearances and signal-averaged ECG (SAECG) in 7 cases with ARVD, and evaluated the usefulness of SAECG as a screening test to detect patients with ARVD. Compared with the conventional 12-lead ECG, the SAECG detects abnormalities at a higher rate in ARVD patients (57% versus 86%). SAECG was more sensitive as a screening test to detect patients with ARVD than 12-lead ECG. (Jpn Heart J 2001; 42: 287-294)

Key words: Electrocardiogram, Late potential, Endomyocardial biopsy

PATIENTS with arrhythmogenic right ventricular dysplasia (ARVD) are at risk for sudden death. ARVD is a heart muscle disorder of unknown etiology that is characterized pathologically by fibrofatty replacement of the right ventricular myocardium.¹⁻⁴⁾ Segmental right ventricular disease is usual, but evolution to more diffuse right ventricular involvement and left ventricular abnormalities with heart failure also have been reported.⁵⁻⁸⁾ Familial occurrence is frequent, and several specific genetic abnormalities have recently been described.⁹⁻¹³⁾

The pathophysiology underlying this disease is unknown. Similarly, the hemodynamic changes and arrhythmogenic profile associated with ARVD have not been systematically studied. The present study used signal-averaged electrocardiography (SAECG) as a screening test to identify patients who have ARVD and to determine the clinical significance of this disorder. Among several ways to analyze the SAECG, we selected the vector magnitude method of Ozawa, *et al.*¹⁴⁾ This method is widely used in Japan and its normal distributions have already been reported in a Japanese population.¹⁵⁾

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METHODS

The study included 7 patients (2 men and 5 women, 16 to 70 yr.). The diagnosis of ARVD was made based on criteria published by McKenna, *et al.*¹⁶⁾ These criteria are subdivided into major and minor criteria and are classified into six categories based on identification of the following: 1) global and/or regional dysfunction and structural alternations, 2) fatty or fibrofatty replacement of the right ventricular free wall, 3) repolarization abnormalities, 4) depolarization/conduction abnormalities, 5) arrhythmia and 6) family history. The diagnosis was based on the presence of the two major criteria; one major plus two minor criteria; or four minor criteria. Patients presenting with complete right bundle branch block on the surface electrocardiogram were excluded because this conduction defect can mask late potentials, as demonstrated by Omen, *et al.*¹⁷⁾ As controls, we selected 241 patients who had no known heart disease and whose mean age was 25.8±9.9, (85 men and 156 women).

SAECG: A SAECG in the time domain was performed using a Marquette MAC 15 system (18-20) to record standard orthogonal leads X, Y, and Z. The signals from the 3 leads were bandpass-filtered digitally with a high-pass bi-directional filter (40 Hz). The low-pass cutoff frequency was 250 Hz. The signals were combined into a vector magnitude waveform, V ($V = x^2 + y^2 + z^2$). The following indexes were derived from this waveform of the filtered QRS: total filtered QRS duration (fQRS), the root-mean-squared voltage of the terminal 40 ms (RMS), and the duration of low amplitude signals (LAS) <40 μ V in the terminal portion of the filtered QRS. As reported by Timmermans, *et al* using a 40 Hz high-pass filter, the normal values were: fQRS <122 ms for men; fQRS <115 ms for women; LAS <41 ms and RMS >20 μ V for both genders. Late potentials were considered positive if at least 2 of the above-mentioned variables were positive. We selected the vector magnitude method of Ozawa, *et al.*¹⁴⁾ and showed the criteria in comparison with other reports (Table I).

Echocardiography: An echocardiogram was performed in all patients to evaluate right ventricular structural abnormalities and to measure right ventricular end-diastolic diameter and left ventricular ejection fraction. From M-Mode record-

Table I. Diagnostic Criteria of Late Potential by a Vector Magnitude Method¹²⁾

Authors	High-pass filter (Hz)	Filtered QRS duration (msec)	Root means square voltage (μ V)	Low amplitude signal (msec)
Simon, <i>et al</i>	25	>110	and >25	
Gomes, <i>et al</i>	40	>114	or <25	under 40 μ V >38
Kucher, <i>et al</i>	40	>120	or <20	
Nalos, <i>et al</i>	absolute 100	>120		under 20 μ V >30
Ozawa, <i>et al</i>	40	>120	or <20	under 40 μ V >40

ings, the thickness of the left ventricular wall and left ventricular dimensions were measured using American Society of Echocardiography standards.²¹⁾

Arrhythmic patterns: Serial basal electrocardiograms and Holter monitoring were performed in all patients to assess electrical instability. Ventricular arrhythmias, occurring before admission and before SAECG and endomyocardial biopsy, were considered representative of the patient's arrhythmic profile. There were 4 patients with sustained ventricular tachycardia or ventricular fibrillation and 2 patients with non-sustained ventricular tachycardia.

Angiography: Angiographic studies were performed in 5 cases, and included an evaluation of right ventricular morphology.^{21,22)} Left ventricular end-diastolic volume and ejection fraction were also determined. Coronary angiograms were performed to detect ischemic heart disease.

Endomyocardial biopsy: Endomyocardial biopsies of the right ventricle were obtained in 6 patients via a femoral vein approach using the long sheath technique. The samples were obtained at the junction between the ventricular septum and the anterior free wall, close to the apex. One to 3 biopsy specimens were obtained from each patient, fixed in 10% phosphate-buffered formalin, and then processed for histologic examination. The biopsied tissues were graded for the severity of fatty involvement and fibrosis using the following scale: mild, lesions involving less than 25% of the ventricular myocardium; moderate, lesions involving 25 to 50% of the myocardium; and severe, lesions involving 50 to 75% of the myocardium; and very severe, lesions involving 75 to 100% of the myocardium. Paraffin-embedded sections were serially cut and stained with hematoxylin-eosin. Abnormal values were established from a control group of transplanted patients: a percentage of myocytes <63%, a percentage of fatty tissue >3%, and a percentage of fibrous tissue >15%.^{23,24)}

RESULTS

The main electrocardiographic, echocardiographic, Holter monitoring, SAECG, and histologic findings are presented in Table II.

12-lead ECGs and late potentials: These patients had 12-lead ECG abnormalities (50%). Of the controls, 12 of 242 patients had ECG abnormalities, including an epsilon wave-like pattern (Figure 1) or nonspecific ST-T changes (5%). Five patients had late potentials using a 40-Hz filter (Figure 2). Nineteen of the 241 control patients also had late positive late potentials (8%).

Arrhythmic profile: The most severe spontaneous ventricular arrhythmias, recorded before admission, are summarized in Table II. Ventricular fibrillation was documented in 1 patient and sustained ventricular tachycardia in 3 cases. None of the control cases had severe spontaneous ventricular arrhythmias.

Figure 1. Electrocardiography in Patient No. 1 demonstrated epsilon waves (arrows) in V1 and V2.

Figure 2. Patient No.3 had the positive late potentials as 40-HZ filter (fQRS = 165 ms, LAS = 106 ms, RMS = 4 μ V).

Histologic biopsy findings: Fatty tissue was observed in the biopsy specimen from 4 of the patients in whom right ventricle biopsies were performed (Figure 3). Interstitial fibrosis was also seen in 4 of these 6 patients, as shown in Table II.

DISCUSSION

Table II. Clinical Findings in Six Patients with ARVC

Case No.	1	2	3	4	5	6	7
Electrocardiography	Epsilon Negative T	Normal	Epsilon Negative T	Negative T	Normal	Normal	QRS widening
Late potential Holter monitoring	Positive SVT	Positive SVT	Positive NSVT	Positive NSVT	Negative SVT	Positive SVT	Positive VF
Right ventricle by echocardiography	Dilated	Dilated	Dilated	Dilated	Dilated	Normal	Dilated
Biopsied specimen							
Fatty replacement	Severe	Mild	Moderate	ND	ND	Mild	Moderate
Fibrosis	Mild	Mild	Moderate	ND	ND	Moderate	Moderate

SVT = sustained ventricular tachycardia; NSVT = non-sustained ventricular tachycardia; ND = not done.

Left ventricle

Right ventricle

X400

X200

Figure 3. Patient No.1 had sustained ventricular tachycardia and a dilated right ventricular ventricle. Right ventricular biopsy samples showed significant fibrosis and extensive fatty infiltration. The left ventricle shows mild myocardial degeneration in the biopsied specimen.

This study shows that SAECG can be useful as a screening test to detect patients with ARVD, in addition to Holter monitoring, echocardiography, and myocardial biopsies. Although the number of patients in the study was small, the sensitivity of SAECG was significant.

ARVD is recognized clinically as recurrent ventricular tachycardia of right ventricular origin and a cardiomyopathy limited to the right ventricle.¹⁻⁶⁾ Localized hypokinesia in the right ventricle is usually demonstrated, and the right ventricle may be dilated. There is excessive adipose tissue in the subepicardium. Patients with ARVD have recurrent episodes of ventricular tachycardia with a left bundle branch block-like pattern that can usually be induced by electrical stimulation, suggesting a reentrant mechanism. Fragmented or delayed potentials are often recorded during endocardial mapping of the right ventricle.²⁵⁾ These areas of slow conduction, in conjunction with endomyocardial biopsy findings of fatty infiltration, a decrease in myocardial fibers, and intramyocardial fibrosis in the dysplastic right ventricle, may cause inhomogeneity of activation and recovery and thus, promote reentry.²⁵⁾

ARVD is usually diagnosed in patients between the ages of 20 and 50 years. A familial predisposition for ARVD has been described, suggesting that a genetic factor may be involved.^{1-6, 8-16)} Only 10% of patients are diagnosed before the age of 20, probably because the arrhythmia is not apparent during this stage of life. However, patients with ARVD have an increased risk of cardiac sudden death. These events generally occur during sports activities or strenuous exercise in young adults and may be the first episode of a ventricular arrhythmia.¹⁻⁴⁾ The finding that sudden death occurs even in young people suggests that the juvenile form of ARVD is not benign. Routine clinical examination is often normal, because the standard 12-lead ECG in sinus rhythm shows epsilon waves in only 30% of cases.²⁵⁾ A screening test for detecting patients with ARVD is needed, since the SAECG procedure is neither complicated nor time consuming (about 10 minutes).¹⁵⁾ Moreover, it is cost-effective and only requires 1 meter of recording paper. The reasons why we utilized time domain method instead of frequency domain method to study the SAECG are as follows:^{26,27)} 1) Time domain method is well established and has good reproducibility, 2) Frequency domain method is well utilized. 3) A Marquette MAC 15 system, used in this study, includes the time domain method but not the frequency domain method.¹⁸⁻²⁰⁾

Mehta, *et al*²⁸⁾ reported that in patients with ARVD the extent of abnormality of the SAECG variables is proportional to the degree of right ventricular cavity enlargement and indicative of the severity of right ventricular dysfunction. Turrini, *et al*²⁹⁾ reported that SAECG variables and right ventricular ejection fraction correlate with the extent of myocardial fibrosis on biopsy in ARVD. They

also showed that an increased percentage of fibrous tissue was a significant univariate predictor of late potentials and that reduced right ventricular ejection fraction plays an essential role in the spontaneous manifestation of sustained ventricular arrhythmia. However, relatively mild cases of ARVD may often show no SAECG abnormalities.

In our study the prevalence of late potentials was 86%. Generally, 50 to 80 % of patients with right ventricular dysplasia have abnormal SAECGs, with a specificity in the range of 90 to 100%.³⁰⁾ Kinoshita, *et al*³¹⁾ suggested that an fQRS duration >110 ms or an area ratio 2 (40 to 100 / 0 to 40 Hz) >75, could serve as criteria for screening for detecting patients with ARVD, and reported that these criteria provided a diagnostic sensitivity of 100%, specificity of 94%, and total predictive accuracy of 100%. In this study, we used only the time-domain SAECG, with more common but more restricted criteria, and found only one patient who did not show late potentials. We believe that SAECG is useful for the identification of patients with ARVD.

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