Correlation between the Parameters of Signal-Averaged ECG and Two-Dimensional Echocardiography in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy

Yongwhi Park, M.D.,* Yongkeun Cho, M.D.,† Dong-Yeub Lee, M.D.,‡
Gui-Lyen Jang, M.D.,† Hyunsang Lee, M.D.,§ Dong Heon Yang, M.D.,†
Hun-Sik Park, M.D.,† Shung-Chull Chae, M.D.,† Jae-Eun Jun, M.D.,†
and Wee-Hyun Park, M.D.†

From the *Department of Internal Medicine, Masan Samsung Medical Center, Masan, South Korea; †Department of Internal Medicine, Kyungpook National University Hospital, Daegu, South Korea; ‡Department of Internal Medicine, Daegu Veterans Hospital, Daegu, South Korea; and §Department of Internal Medicine, Gumi Cha Medical Center, Gumi, South Korea

Background: The correlation between parameters of two-dimensional echocardiography and signal-averaged ECG (SAECG) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) is not known well.

Methods: Thirty-three patients (13 females, 40.3 ± 14.4 years old) were included in this study. Both the right and left ventricular dimensions and systolic function were assessed with two-dimensional echocardiography. The SAECG was performed with high-gain amplification and filtered using bidirectional Butterworth filters between 40 and 250 Hz. We evaluated the correlation between the parameters of the SAECG and two-dimensional echocardiography.

Results: The right ventricular (RV) outflow tract was the most frequently ($n = 18$, 54%) involved segment. Six (18%) patients had only mildly decreased RV systolic function. All the other patients had normal RV systolic function. Although localized left ventricular wall motion abnormalities were observed in 14 (42%) patients, the left ventricular ejection fraction was normal in most ($n = 32$, 97%). Late potentials were positive in 22 (63%) patients. There was no significant correlation between parameters of the SAECG and two-dimensional echocardiography for the entire patient population.

Conclusions: The SAECG parameters exhibited no correlation to any of two-dimensional echocardiography parameters in the patients with ARVC. Fragmented electrical activity may develop with no significant relation to the anatomical changes in the patients with ARVC.

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arrhythmogenic right ventricular cardiomyopathy; signal-averaged electrocardiography;
two-dimensional echocardiography

Traditionally, two-dimensional echocardiography has been used for the evaluation of the right and left ventricular size and function, which are important diagnostic criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC). As it is noninvasive and easily repeatable, it may

be the first imaging modality used in the evaluation of patients with suspected ARVC. Some previous reports have shown that the abnormalities observed in the signal-averaged ECG (SAECG) correlate with the severity or extent of the disease.^{1–3} However, most of the studies focused on the

Address for reprints: Yongkeun Cho, M.D., Department of Internal Medicine, Kyungpook National University Hospital, 50 Samduk 2-Ga, Chung-Ku, Daegu, 700-721, South Korea. Fax: 82-53-426-2046; E-mail: choyk@mail.knu.ac.kr

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difference between the mild form and extensive form of the disease, and the extent of the disease was mainly divided by the right ventricular (RV) volume or RV systolic function,¹⁻³ and those studies have even shown inconsistent results.⁴⁻⁵ Considering the early occurrence of sudden death in ARVC patients,⁶⁻⁸ the extent of the abnormalities observed in the SAECG in relation to the extent of the disease may be more important in the mild form or early stages of the disease than in the extensive forms. The purpose of this study was to investigate the correlation between the parameters of the SAECG and two-dimensional echocardiography in patients with ARVC.

MATERIALS AND METHODS

Study Population

The patient population consisted of 38 ARVC patients from the Daegu-Kyungpook area of South Korea who met the task force criteria for ARVC.⁹ Only patients with a normal coronary angiography were included. The details of the clinical characteristics have been published previously.¹⁰ Three patients with bundle branch block, one with a delta wave, and another with noise $>0.3 \mu\text{V}$ on the SAECG were excluded from further study. Finally, 33 patients (13 females, 40.3 ± 14.4 years old) with ARVC were included. The institutional ethics committees approved the study protocol and written informed consent was obtained from each patient.

SAECG

The SAECG was performed using a MAC 15 system (Marquette, Milwaukee, WI, USA) with high-gain amplification and bidirectional Butterworth filters (40–250 Hz). The patients with a noise level $>0.3 \mu\text{V}$ were excluded from the study. Late potentials were considered present if two or more of the three following criteria were met: (1) a filtered QRS duration (fQRS) >114 ms, (2) a low-amplitude ($<40 \mu\text{V}$) signal duration (LAS40) >38 ms, and (3) a root mean square voltage (RMS40) in the terminal 40 ms of the fQRS $<20 \mu\text{V}$.¹¹

Two-Dimensional Echocardiography

Two-dimensional echocardiography was carried out with a Vivid 5 or Vivid 7 (GE, Horten, Norway) using a 2.5-MHz probe. The echocardiographic pa-

rameters were measured according to the usual recommendations.^{12,13} The following measurements were used:

1. RV inflow tract (RVIT)
 - (a) We measured the maximal perpendicular distance from the right side of the mid-interventricular septum to the RV free wall in the parasternal short-axis view of the tricuspid valve (RVIT1).
 - (b) We measured the transverse diameter at a point located one-third the distance between the tricuspid valve annulus and RV apex (RVIT2) in the apical four-chamber view.
2. RV cavity
 - (a) We measured the distance midway between the tricuspid valve annulus and RV apex in the apical four-chamber view (RV SAX).
3. RV outflow tract (RVOT)
 - (a) We measured the distance from the right side of the interventricular septum to the anterior RV free wall in the parasternal long-axis view (RVOT1).
 - (b) We measured the RVOT from a region 2 cm below the pulmonary valve annulus (RVOT2) and from just beneath the pulmonary valve annulus (RVOT3) in the RVOT view, which was visualized after tilting the transducer upward toward the left shoulder from the parasternal long-axis view.
 - (c) We measured the maximal distance between the anterior aortic wall and RV free wall endocardium in the parasternal short-axis view of the aortic root (RVOT4).

All the dimensions of the RV were corrected for the body surface area since a normal reference value of the RV dimension was not available in South Korea. Thus, we compared the two-dimensional echocardiographic results with the previously published reference.¹³ The RV systolic function was assessed from the RV fractional area change (FAC) in the apical four-chamber view.¹³ An RV FAC $\geq 32\%$ was defined as normal, ≥ 26 and $<32\%$ as mildly reduced, and $<26\%$ as severely reduced. The left ventricular (LV) end-diastolic dimensions were measured at the level of the tip of the mitral leaflet from the parasternal long-axis view, using two-dimensional targeted M-mode echocardiography. An LV end-diastolic dimension >5.6 cm was considered abnormal. The LV end-systolic and end-diastolic volumes were measured

by the modified Simpson’s rule from the apical four-chamber view. Those parameters were also compared with the previously published reference.¹² The LV ejection fraction was calculated as follows: ejection fraction = (end-diastolic volume – end-systolic volume)/end-diastolic volume.¹² An ejection fraction $\geq 55\%$ was considered a normal LV systolic function.¹²

Statistical Analysis

We used the Pearson’s chi-square test for the categorical variables and Student t-test for the continuous variables. The two-dimensional echocardiographic parameters were compared with all three SAECG variables using the Pearson’s correlation coefficient and Spearman’s rho. A P value <0.05 was considered statistically significant. SPSS (SPSS Inc, Chicago, IL, USA) version 11.5 was used for all statistical analyses.

RESULTS

Clinical Characteristics of the Patients

The clinical characteristics of the patients are presented in Table 1. Eleven patients (33%) were asymptomatic and were evaluated due to abnormalities of their ECGs taken during routine health checks or before operations. Two patients with a family history of premature sudden death or a diagnosed ARVC were also asymptomatic. The symptoms experienced in the patients included palpitations in 11 (33%), syncope or presyncope in eight (24%), and atypical chest pain in 2 (6%). In the patients with ventricular tachyarrhythmias, palpitations occurred in 4 and syncope in 2. Only 2 patients complained of symptoms or signs of heart

Table 1. Clinical Characteristics of the Patients

Age (years)	40.3 ± 14.4
Sex (male/female)	20/13
Family history	2
Diagnosed ARVC*	1**
Premature sudden death	1
Presenting symptoms	
Palpitations	11 (33%)
Syncope/presyncope	8 (24%)
Atypical chest pain	2 (6%)
Cardiac arrest	1 (3%)
Sudden death in a family member	1 (3%)
None	11 (33%)

*Arrhythmogenic right ventricular cardiomyopathy; **autopsy proven.

failure. Two-dimensional echocardiography and/or selective ventriculography revealed wall motion abnormalities of the right and left ventricles in 31 (94%) and 14 (42%) patients, respectively. The RV global function was normal in 27, mildly reduced in 6, and severely reduced in none. The LV ejection fraction was normal in all except one. Wall motion abnormalities of the RV and the presence of late potentials were essential for the diagnosis of ARVC in 17 (52%) and 8 (24%) patients, respectively.

Routine Evaluations

The routine ECG, Holter monitoring, and exercise ECG revealed ventricular fibrillation (VF) in one, sustained ventricular tachycardia (VT) in five, nonsustained VT in six, frequent (>1,000 beats/24 hours) premature ventricular contractions (PVCs) in thirteen, and only infrequent PVCs in 3.

Two-Dimensional Echocardiography

Table 2 shows the two-dimensional echocardiographic results in the patients. An enlarged RVOT

Table 2. The Two-Dimensional Echocardiographic Right Ventricular Dimension and Volume Measurements

	Absolute Values	Corrected Values for BSA	Frequency of Abnormalities (%)
RVIT1 (cm)	2.6 ± 0.4	1.5 ± 0.2	0
RVIT2 (cm)	3.2 ± 0.6	1.9 ± 0.3	42
RVOT1 (cm)	3.0 ± 0.6	1.7 ± 0.3	54
RVOT2 (cm)	2.4 ± 0.3	1.4 ± 0.2	0
RVOT3 (cm)	2.3 ± 0.4	1.4 ± 0.2	39
RVOT4 (cm)	3.0 ± 0.4	1.8 ± 0.2	18
RV SAX (cm)	3.0 ± 0.4	1.7 ± 0.3	9
RVEDA (cm ²)	22.0 ± 4.4		3
RVESA (cm ²)	13.1 ± 3.6		24
FAC (%)	40.9 ± 8.3		18
LVEDD (cm)	4.8 ± 0.6		3
LVEDV (mL)	87.1 ± 20.5		0
LVESV (mL)	33.5 ± 9.7		0
LVEF (%)	61.4 ± 5.1		3

BSA = body surface area (m²); RVIT = right ventricular inflow tract; RVOT = right ventricular outflow tract; RV SAX = middle third of the right ventricle in the apical four-chamber view; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; FAC = fractional area change; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction.

Table 3. Comparison of the Two-Dimensional Echocardiographic Parameters According to the Presence of ECG Abnormalities and Arrhythmias

	VT/VF			Depolarization/Repolarization Abnormalities*		
	Present	Absent	P	Present	Absent	P
RVIT1 (cm)	2.7 ± 0.5	2.5 ± 0.4	0.29	2.5 ± 0.5	2.6 ± 0.4	0.54
RVIT2 (cm)	3.3 ± 0.7	3.2 ± 0.5	0.58	3.3 ± 0.6	3.2 ± 0.5	0.67
RVOT1 (cm)	3.2 ± 0.3	2.9 ± 0.6	0.36	2.8 ± 0.6	3.1 ± 0.5	0.14
RVOT2 (cm)	2.5 ± 0.2	2.4 ± 0.3	0.41	2.5 ± 0.4	2.4 ± 0.3	0.78
RVOT3 (cm)	2.5 ± 0.4	2.3 ± 0.4	0.10	2.4 ± 0.4	2.3 ± 0.3	0.52
RVOT4 (cm)	3.1 ± 0.2	3.0 ± 0.5	0.55	2.9 ± 0.5	3.1 ± 0.4	0.09
RV SAX (cm)	2.9 ± 0.5	3.0 ± 0.3	0.82	3.0 ± 0.4	2.9 ± 0.3	0.80
RVEDA (cm ²)	20.6 ± 5.7	22.3 ± 4.1	0.39	21.9 ± 4.5	22.2 ± 4.4	0.88
RVESA (cm ²)	12.7 ± 4.6	13.3 ± 3.4	0.77	13.5 ± 3.5	12.7 ± 3.8	0.55
FAC (%)	39.3 ± 5.3	41.2 ± 9.0	0.62	38.9 ± 7.4	43.3 ± 9.0	0.14
LVEDD (cm)	4.9 ± 0.5	4.8 ± 0.6	0.72	4.9 ± 0.6	4.8 ± 0.6	0.78
LVEDV (mL)	86.4 ± 24.1	87.2 ± 20.1	0.93	85.5 ± 22.3	88.9 ± 18.6	0.64
LVESV (mL)	32.5 ± 13.9	33.8 ± 8.8	0.77	32.8 ± 10.6	34.4 ± 8.7	0.65
LVEF (%)	62.8 ± 7.4	61.1 ± 4.6	0.46	61.6 ± 5.0	61.3 ± 5.4	0.87

*Including epsilon waves, localized prolongation (>110 ms) of the QRS complex in the right precordial leads, and inverted T waves in the right precordial leads.

VT = ventricular tachycardia; VF = ventricular fibrillation; RV = right ventricle; P = probability value; other abbreviations are as in Table 2.

dimension in the parasternal long-axis view was the most frequently observed abnormality (54%). Enlargement of the RVIT dimension in the apical four-chamber view was also observed in about half (48%) of the patients. The RV SAX in the apical four-chamber view was rarely enlarged (9%). Localized wall motion abnormalities of the RV were mostly observed in the apex (48%). Only one patient had an enlarged RV end-diastolic area. However, abnormal RV end-systolic areas and FACs were observed in 8 (24%) and 6 (18%) patients, respectively. All the patients with an abnormal FAC had only a mildly reduced RV systolic function (mean $28.6 \pm 1.8\%$). Wall motion abnormalities of the LV were observed in 14 (42%). However, as those wall motion abnormalities were small and localized at the apex and/or anterior wall in most patients, the mean LV ejection fraction was $61.4 \pm 5.1\%$. The LV end-diastolic dimension was >5.6 cm in one. None of the patients had abnormal LV end-diastolic or end-systolic volumes. Only one patient had an LV ejection fraction $<55\%$. The presence of sustained VT/VF or depolarization/repolarization abnormalities in the ECG was not associated with any differences in the two-dimensional echocardiographic parameters. The patients with ventricular arrhythmias satisfying the minor criteria of the task force exhibited somewhat larger RVOT dimensions than those without (2.9 ± 0.5 vs 3.1 ± 0.4 cm,

$P = 0.09$; Table 3). Six patients with a reduced FAC had a larger RV SAX dimension than those with a normal FAC (3.2 ± 0.2 vs 2.9 ± 0.4 cm, $P = 0.03$). However, there was no difference in any of the other dimensions between the patients with a normal and those with a reduced RV systolic function.

SAECG

Table 4 shows the results of the SAECGs. Late potentials were positive in 22 (63%) patients. The fQRS was abnormal in 21 (64%) patients, LAS40 in 19 (58%), and RMS40 in 17 (52%). Among 6 patients with sustained VT/VF, abnormal SAECGs were documented in 4 (67%) patients. The presence of sustained VT/VF or ventricular arrhythmias satisfying the minor criteria of the task force was not associated with any differences in the SAECG parameters. The presence of depolarization/repolarization abnormalities such as inverted T waves in the right precordial leads, a wide QRS complex in leads V_1 – V_3 , or epsilon waves also did not result in a significant difference in the parameters of the SAECG (Table 4). The extent of the abnormalities on the SAECG had no correlation with any two-dimensional echocardiographic parameters for either ventricle in any of the patients (Table 5). Only the fQRS was significantly

Table 4. Comparison of the Signal-Averaged ECG Parameters According to the ECG Abnormalities, Arrhythmias, and Right Ventricular Systolic Function

	VT/VF			Depolarization/Repolarization Abnormalities*			RV Systolic Function**		
	Present	Absent	P	Present	Absent	P	Normal	Reduced	P
fQRS	118.7 ± 11.4	119.7 ± 13.7	0.86	121.9 ± 14.1	116.7 ± 11.8	0.27	125.3 ± 19.5	118.3 ± 11.5	0.24
LAS40	41.0 ± 12.3	43.3 ± 12.3	0.70	44.0 ± 14.5	41.6 ± 11.8	0.60	50.7 ± 20.7	41.2 ± 10.7	0.11
RMS40	24.3 ± 14.1	23.8 ± 15.5	0.93	22.0 ± 11.5	26.1 ± 18.7	0.45	21.0 ± 13.3	24.5 ± 15.6	0.59

*Including epsilon waves, localized prolongation (>110 ms) of the QRS complex in the right precordial leads, and inverted T waves in the right precordial leads; right ventricular fractional area change ≥ 32% was defined as normal and, <32% as reduced.

fQRS = filtered QRS duration; LAS40 = low-amplitude (<40 µV) signal duration; RMS40 = root mean square voltage of the terminal 40 ms; VT = ventricular tachycardia; VF = ventricular fibrillation; RV = right ventricle.

correlated to the RV end-diastolic area and RV end-systolic area in the selective patients with VT/VF ($r = 0.943$, $P = 0.005$ for RV end-diastolic area; $r = 0.886$, $P = 0.019$ for RV end-systolic area). However, it was not correlated with the LV end-diastolic or end-systolic volume in those patients ($r = 0.371$, $P = 0.468$ for LV end-diastolic volume; $r = 0.086$, $P = 0.872$ for LV end-systolic volume).

DISCUSSION

This study may be considered as the first comprehensive two-dimensional echocardiographic and SAECG evaluation in Asian patients with ARVC. Similar to the data of the American registry,¹⁴ an enlarged RVOT dimension was the most prevalent finding in this study. However, the other dimensions of the RV, including the RVOT, were smaller than those in the American registry. Although right atrial and RV enlargement and a decreased RV systolic function were prevalent findings in the American Registry, that was not the case in this study. The patients in this study had a better RV systolic function and there were more patients with no or minimal symptoms than those in the American Registry. This may be helpful for explaining the differences between the two studies.

There is some possibility that the patients in this study may have represented the real clinical characteristics of the patients with ARVC, similar to the report from Germany,¹⁵ as most were diagnosed from one center and many were asymptomatic or minimally symptomatic. And also, Nava et al. reported that the majority of affected family members of ARVC had the mild form of the disease and just segmental RV involvements with normal RV volume.⁶ These findings suggested that the localized pathological changes of the disease may be manifested only as an increased fragmented electrical activity with no detectable changes or abnormalities observed in the two-dimensional echocardiography in at least some patients with ARVC.

In the present study, there were no consistent correlations between the SAECG variables and two-dimensional echocardiographic parameters. In addition, we could not find any significant differences in those parameters between the patients with a normal and reduced RV systolic function. The pathological changes in the myocardium may initially be localized to limited areas and might not produce any detectable RV enlargement or aneurysmal formations in the two-dimensional

Table 5. Correlation between the Signal-Averaged ECG and Two-Dimensional Echocardiography Parameters

	RVOT				RVIT		RV SAX	RVEDA	RVESA	FAC
	1	2	3	4	1	2				
fQRS										
r coeff	-0.22	-0.32	-0.18	-0.24	-0.06	-0.07	0.26	0.09	0.10	-0.1
P	0.22	0.07	0.32	0.18	0.74	0.69	0.14	0.61	0.59	0.58
LAS40										
r coeff	-0.19	-0.30	-0.21	-0.21	-0.10	-0.26	0.18	-0.10	-0.05	-0.09
P	0.30	0.09	0.25	0.23	0.58	0.15	0.33	0.60	0.77	0.62
RMS40										
r coeff	0.15	0.29	0.14	0.18	0.15	0.16	-0.06	0.01	0.07	-0.10
P	0.40	0.11	0.42	0.32	0.42	0.37	0.73	0.98	0.69	0.56

coeff = coefficient; other abbreviations are as in Tables 2 and 4.

echocardiography.^{6-8,16} However, the late potentials on the SAEKG are known to originate from the electrical discontinuity caused by the fibrofatty infiltration and fragmentation of the ventricular depolarization.² Therefore, the late potentials on the SAEKG might be present with only small pathological changes of the myocardium. Considering many patients in this study exhibited only small and localized wall motion abnormalities in the two-dimensional echocardiography, correlation between the SAEKG variables and two-dimensional echocardiographic parameters might have been absent in those kinds of patients with a preserved RV systolic function or volume.

Another interesting finding in this study was that whether they suffered from VT/VF or not, there was no difference in the abnormalities of the SAEKG. Although some previous studies revealed a close correlation between at least one of the SAEKG parameters and the presence of documented sustained VT,^{1,2} there has been much debate on whether the SAEKG parameters correlate with the presence of VT/VF even in the patients with normal or mildly dilated RV end-diastolic volumes, which is the so-called mild form of the disease.^{5,7} The VTs in mild form of the disease usually exhibit a left bundle branch block morphology and inferior axis.⁴ They may be related to the absence of late potentials because of their very low-amplitude potentials or concealed late potentials in the QRS complex.^{2,4} Moreover, although reentry is the most important mechanism for the occurrence of VTs in the patients with ARVC,¹⁷ late potentials recorded in the SAEKG are not specific for reentrant ventricular tachyarrhythmias and are better correlated with an extension of the RV involve-

ment.^{1,3,4} In addition to the reentry circuit of the degenerated myocardium, triggered events or modulating factors such as sympathetic stimuli may be essential for the development of VTs in patients with ARVC.^{3,5,16,18,19} Therefore, the presence of VT may not have significant effect on the SAEKG parameters. The prevalence of late potentials was relatively high in this study, considering that many of the patients in this study were asymptomatic or complained only of atypical chest pain.^{1,2,4} This finding also supports the poor correlation between the SAEKG abnormalities and the presence of VT.

In this study, about one third of the patients had no symptoms. They were just referred for further evaluation based on an abnormal ECG. Thus, this cohort probably deviated toward the patients with very early disease, who will not have significant RV dilatation. Nonetheless, a large percentage of the patients had the abnormal SAEKG results. The reasons for the high prevalence (63%) of positive late potentials are not well understood. Traditional concepts of ARVC have suggested that anatomical barriers of conduction such as myocardial fibrofatty replacement may manifest as a prolonged conduction or late potentials.² However, the recent animal study showed that spontaneous VT and a prolonged RV conduction time could occur even without the histological changes in the myocardium in heterozygous plakoglobin-deficient mice.¹⁶ This suggests that a diminished mechanical adhesion between the cardiomyocytes themselves may also manifest as a diminished electrical conduction and the late potentials on the SAEKG with no relation to the presence of a fibrofatty infiltration.

Because of the diverse possibilities of the ventricular arrhythmias and difficulties in the pathological

diagnosis of ARVC in living patients, the relationship between the functional and structural changes in ARVC is still not fully understood.¹⁹ Therefore, further studies are needed to clarify the relationship between the functional and structural changes in patients with ARVC.

Our study has a few limitations. First, this was a single center study composed of a substantial number of patients enrolled from routine health care or preoperative evaluations. Thus, the late potentials on the SAEKG and RV wall motion abnormalities played an important role in diagnosing the ARVC. Those might have resulted in a source of selection bias. Second, we performed only a time-domain analysis with a 40–250-Hz filter setting. Third, no genetic studies were available in this study.

Despite a few limitations, the parameters of the SAEKG showed no correlation to the two-dimensional echocardiographic parameters. It suggests that fragmented electrical activity may appear with no significant relation to the anatomical alterations in patients with ARVC.

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