

Value of Quantitative Measurement of Signal-Averaged Electrocardiographic Variables in Arrhythmogenic Right Ventricular Dysplasia: Correlation With Echocardiographic Right Ventricular Cavity Dimensions

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Objectives. We sought to investigate the relation between signal-averaged electrocardiographic (ECG) variables and the extent of right ventricular disease, as estimated by right ventricular enlargement during detailed echocardiography, in patients with arrhythmogenic right ventricular dysplasia.

Background. In patients with ventricular tachycardia of right ventricular origin, a normal signal-averaged ECG is indicative of "idiopathic" ventricular tachycardia, whereas an abnormal signal-averaged ECG is a specific marker for right ventricular disease, especially dysplasia. Signal-averaged ECGs in these patients are mildly to grossly abnormal.

Methods. Ten patients with the clinical diagnosis of arrhythmogenic right ventricular dysplasia were included. All patients had documented, sustained ventricular tachycardia, no coronary artery disease and a normal QRS duration of ≤ 110 ms on routine 12-lead electrocardiography. Signal-averaged ECGs were recorded using time-domain analysis. Right ventricular cavity dimensions recorded during two-dimensional echocardiography were measured at the level of the inflow tract, midcavity and outflow tract. Signal-averaged ECG variables and echocardiographic

measurements were correlated using linear regression analysis.

Results. Nine of 10 patients had abnormal signal-averaged ECGs. There was a consistent correlation between all signal-averaged ECG variables and the right ventricular cavity dimensions at the level of the midcavity. The correlation was most significant with the duration of the filtered QRS complex ($p < 0.001$ for QRS duration, $p < 0.01$ for late potential duration and $p < 0.05$ for root-mean-square voltage of the last 40 ms). There was no consistent correlation between the signal-averaged ECG variables and right ventricular dimensions at the level of the inflow and outflow tracts.

Conclusions. The majority of patients with arrhythmogenic right ventricular dysplasia have abnormal signal-averaged ECGs. In the absence of bundle branch block, the extent of abnormality of signal-averaged ECG variables is in proportion to right ventricular cavity enlargement, and thus is indicative of the severity of right ventricular dysfunction.

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In young patients, subclinical right ventricular dysplasia can present as sudden death, particularly during exercise and competitive sports (1-3). More frequently, the initial presentation is ventricular premature beats or nonsustained ventricular tachycardia. In the latter group of patients, ST and T wave changes in the right-sided precordial leads of a 12-lead electrocardiogram (ECG) or an abnormal signal-averaged ECG have been shown to be specific markers for right ventricular dysplasia (4-8). Signal-averaged electrocardiography is used

to detect low amplitude, high frequency components in the terminal QRS complex using time-domain and frequency analysis (9). In patients with ventricular tachycardia of right ventricular origin, these signals represent areas of slow conduction and are a specific marker for right ventricular dysplasia. Fifty to eighty percent of patients with right ventricular dysplasia have abnormal signal-averaged ECGs with a specificity in the range 90% to 100% (10-13). However, the significance of the extent of abnormality of signal-averaged ECG variables in relation to the extent of right ventricular disease is not known. In the present study the signal-averaged ECG variables were correlated with the extent of right ventricular disease, as defined by right ventricular cavity dimensions during two-dimensional echocardiography.

Methods

Ten patients (mean age 41 years, range 22 to 62) with documented, sustained monomorphic ventricular tachycardia

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were included in the study. Patients with ventricular tachycardia of left bundle branch block-like configuration, with evidence of right ventricular enlargement to suggest right ventricular dysplasia on routine echocardiography, were included in the study. All patients had normal coronary arteries and normal left ventricular function, as documented by coronary angiography and left ventriculography. Patients with an intraventricular conduction delay (QRS duration >110 ms) or a prolonged QT interval were excluded in order to exclude those with severe right ventricular dysplasia, because there is no doubt about the clinical diagnosis when intraventricular conduction delay or right bundle branch block is present. Thus, only patients considered to have early disease were included.

Right ventricular echocardiograms were performed using a previously described technique with the investigators blinded to the signal-averaged ECG findings (14,15). High resolution, M-mode and two-dimensional images were obtained with a 2.5- or 3.5-MHz transducer (Acuson and Hewlett Packard, 1500), recorded on videotape and analyzed. Long-axis, short-axis and apical views were acquired according to the standard of the American Society of Echocardiography. Long- and short-axis views were obtained in the left parasternal window, cardiac apex and suprasternal locations. Measurements of the right ventricle were obtained at the inflow, body and outflow tracts in end-diastole frames recorded with respiration held in end-expiration (15). The following measurements were used.

Right ventricular inflow tract. 1) In the parasternal long-axis view of the left heart, the transducer was tilted medially and downward to image the right ventricular inflow tract and the right ventricular body in the long axis. The tricuspid valve and right ventricular apex were used as reference points. The measurement was taken at one-third the distance below the tricuspid annulus toward the region of the right ventricular apex.

2) In the parasternal short-axis view of the mitral valve, this was the maximal perpendicular distance from the right side of the interventricular septum to the right ventricular free wall.

3) In the standard apical four-chamber view, this was the transverse diameter at a point located at one-third the distance between the tricuspid valve annulus and the right ventricular apex.

Right ventricular cavity. In the apical four-chamber view, this measurement was obtained midway between the tricuspid annulus and the apex of the right ventricular cavity.

Right ventricular outflow tract. 1) In the left parasternal long-axis view, this was the distance from the right side of the interventricular septum to anterior right ventricular free wall.

2) In the true long-axis view, this was measured as the maximal transverse diameter 2 cm below the pulmonary valve annulus.

3) In the true long-axis view, this was measured as the maximal diameter just beneath the pulmonary valve.

4) On the parasternal short-axis view of the aortic root, this was measured as the maximal distance between the anterior aortic annulus and the right ventricular free wall endocardium.

Signal-averaged electrocardiography. Signal-averaged ECGs were recorded in sinus rhythm using the Arrhythmia Research Technology system (model No 1200 EPX). Electrocardiograms were recorded in sinus rhythm in a drug-free state; 150 to 300 beats were averaged to obtain a noise level <0.5 μ V. High bandpass filter was fixed at 25 Hz. The duration of the filtered QRS complex, the duration of the late potentials <40 μ V and the root-mean-square voltage of the last 40 ms were analyzed by the computer and printed. They were defined as abnormal if the QRS duration was >114 ms, the duration of the late potential was \geq 32 ms and the root-mean-square voltage of the last 40 ms was \leq 25 μ V (16,17). Late potentials were said to be present if any two of the above three criteria were in the abnormal range.

Statistical analysis. Each right ventricular echocardiographic dimension was correlated with all three signal-averaged ECG variables using linear regression and correlation analysis. A p value <0.05 was considered statistically significant.

Results

Patient age, significant symptoms, ECG findings, QRS configuration and rate of documented ventricular tachycardia are shown in Table 1. All patients were symptomatic and were referred for further management of sustained ventricular arrhythmia. Five patients had experienced syncope related to ventricular tachycardia. The 12-lead ECGs in sinus rhythm showed peak p waves suggestive of right atrial enlargement in two patients (Patients 7 and 8). The QRS duration and configuration were normal in all patients, because patients with a prolonged QRS duration were excluded from the study. Five patients had ST or T wave changes, or both, in the right ventricular leads (Patients 3, 5, 7, 8, and 10). The QRS configuration during ventricular tachycardia was left bundle branch block-like in all patients, suggesting ventricular tachycardia of right ventricular origin (18). The frontal plane axis of ventricular tachycardia was superior in eight patients (80%) and inferior in the other two (20%). Patient 7 had two different configurations, both having a different frontal plane axis.

On echocardiography, all patients had normal left ventricular function (mean \pm SD left ventricular ejection fraction $54 \pm 8\%$) and evidence of right ventricular dysfunction with wall motion abnormalities. Right ventricular cavity dimensions, as compared with those of previously reported normal subjects (14), were increased at two or more sites in all patients. Enlargement of the right atrium was seen in seven patients.

Signal-averaged ECG variables are shown in Table 2. Except for Patient 7, all patients had abnormal signal-averaged ECGs with evidence of late potentials, as defined by conventional criteria (17). The QRS duration was abnormal in six patients (60%), the duration of late potentials was abnormal in nine (90%) and the root-mean-square voltage was abnormal in nine (90%). Figure 1 shows an abnormal signal-averaged ECG

Table 1. Demographic Data, Symptoms, Electrocardiographic Features and Rate of Ventricular Tachycardia in Study Patients

| Pt No. | Age (yr)/Gender | Symptoms* | ST Wave Changes | VT Configuration (BBB/axis) | VT Rate (beats/min) |
|--------|-----------------|------------------------|-----------------|-----------------------------|---------------------|
| 1 | 22/M | Syncope | - | LB, LA | 220 |
| 2 | 26/M | Syncope | - | LB, RA | 230 |
| 3 | 37/M | Syncope | + | LB, LA | 220 |
| 4 | 62/M | Presyncope, sweating | - | LB, LA | 150 |
| 5 | 44/F | Syncope | + | LB, RA | 300 |
| 6 | 46/M | Presyncope, chest pain | - | LB, LA | 250 |
| 7 | 29/M | Syncope | + | LB, LA | 280 |
| | | | | LB, RA | 225 |
| 8 | 39/F | Presyncope | + | LB, LA | 140 |
| 9 | 59/M | Palpitations only | - | LB, LA | 180 |
| 10 | 50/F | Presyncope | + | LB, LA | 160 |

*All patients had palpitations; symptoms shown are those other than palpitations. axis = frontal plane axis of documented ventricular tachycardia; BBB = bundle branch block configuration of documented ventricular arrhythmia; LA = left or superior axis; LB = left bundle branch block-like configuration; Pt = patient; RA = inferior frontal plane axis; VT = clinically documented ventricular tachycardia.

(by all three variables) with a QRS duration <110 ms on 12-lead electrocardiography.

Table 3 shows the linear regression analysis of all right ventricular dimensions at the level of the inflow tract, cavity and outflow tract with signal-averaged ECG variables. There was a statistically significant correlation between right ventricular dimensions at the level of the cavity (Table 3, Fig. 2) and all three signal-averaged ECG variables. The correlation was most significant with the duration of the filtered QRS complex ($p < 0.001$ for QRS duration, $p < 0.01$ for late potential duration and $p < 0.05$ for root-mean-square voltage of the last 40 ms). The correlation of late potential duration and right ventricular body diameter is made more significant by the data from Patient 8 (Fig. 2B). Exclusion of this patient decreases the significance from $p < 0.01$ to $p < 0.05$. Right ventricular inflow and outflow tract dimensions did not show consistent correlation with signal-averaged ECG variables. Only right ventricular inflow tract 3 and right ventricular outflow tract 1

measurements showed a mildly significant correlation with the duration of the filtered QRS complex. In addition to right ventricular cavity dimension, root-mean-square voltage also showed correlation with right ventricular inflow tract 3 and right ventricular outflow tract 4 measurements. Thus, these data indicate that in patients with right ventricular dysplasia, prolongation of the duration of the filtered QRS complex and late potentials and a decrease in root-mean-square voltage are directly proportional to the degree of right ventricular cavity enlargement during echocardiography. The duration of the filtered QRS complex is the most useful variable because it correlates best with the right ventricular cavity dimensions.

Discussion

Diagnosis of right ventricular dysplasia. Right ventricular dysplasia is a well recognized cause of sudden cardiac death in young people (1-3). The diagnosis is always considered in

Table 2. Echocardiographic Dimensions and Signal-Averaged Electrocardiographic Variables in All Ten Patients

| Pt No. | RVI (cm) | | | RVB (cm) | RVOT (cm) | | | | QRSd (ms) | LPD40 (ms) | RMS40 (μV) |
|--------|----------|-----|-----|----------|-----------|-----|-----|-----|-----------|------------|-------------------|
| | 1 | 2 | 3 | | 1 | 2 | 3 | 4 | | | |
| 1 | 4.0 | 3.8 | 4.1 | 3.8 | 2.8 | 2.9 | 2.8 | 3.5 | 137 | 40 | 13 |
| 2 | 5.4 | 3.5 | 3.0 | 3.4 | 2.8 | 2.9 | 4.5 | 5.4 | 124 | 47 | 23 |
| 3 | 3.8 | 2.8 | 3.1 | 3.5 | 3.0 | 2.7 | 2.8 | 3.5 | 113 | 44 | 12 |
| 4 | 6.7 | 4.2 | 4.1 | 4.5 | 4.0 | 3.5 | 3.1 | 4.6 | 153 | 49 | 15 |
| 5 | 3.4 | 2.5 | 2.4 | 2.2 | 2.0 | 2.7 | 2.0 | 2.7 | 108 | 31 | 23 |
| 6 | 5.6 | 3.8 | 3.9 | 2.9 | 3.0 | 2.8 | 2.5 | 3.0 | 119 | 40 | 14 |
| 7 | 4.7 | 3.7 | 3.1 | 2.9 | 3.2 | 3.3 | 3.1 | 3.6 | 104 | 27 | 35 |
| 8 | 6.0 | 4.4 | 4.2 | 5.8 | 3.8 | 3.6 | 4.6 | 5.8 | 235 | 183 | 5 |
| 9 | 4.9 | 4.2 | 4.1 | 4.2 | 3.9 | 3.1 | 2.7 | 3.6 | 209 | 77 | 6 |
| 10 | 4.2 | 4.8 | 2.9 | 2.3 | 3.0 | 3.4 | 3.0 | 3.9 | 103 | 40 | 17 |

LPD40 = duration of the late potentials; QRSd = duration of filtered QRS complex; RMS40 = root-mean-square voltage of last 40 ms; RVB = right ventricular body dimensions at midcavity/base; RVI = right ventricular inflow tract dimensions, as described in text; RVOT = right ventricular outflow tract dimensions, as described in text.

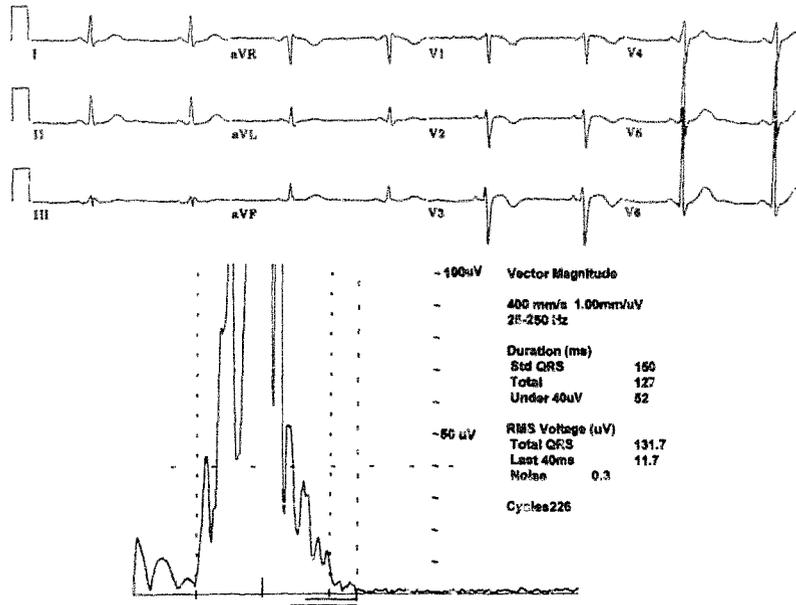


Figure 1. The 12-lead and signal-averaged electrocardiograms (ECGs) from Patient 9. The 12-lead ECG shows mild intraventricular conduction delay; however, the signal-averaged ECG variables are grossly abnormal, with distinct late potentials. Right ventricular cavity dimensions were significantly increased (Table 2). RMS = root mean square.

patients presenting with ventricular tachycardia of right ventricular origin (2,5). In advanced disease the diagnosis is easy to make because there is marked dilation of the right ventricle and possible aneurysm formation with normal left ventricular size and function. However, at an early stage, differentiation from idiopathic right ventricular tachycardia is difficult, although important, because the idiopathic form has a good long-term prognosis and is amenable to catheter ablative therapy (5,19).

The value of angiography, echocardiography, magnetic resonance imaging (MRI) and computed tomography of the right ventricle to diagnose early right ventricular disease has been assessed extensively (20-22). Satisfactory variables have

yet to be defined for angiographic assessment of the right ventricle, because marked trabeculation makes defining the cavity size very difficult. Leclercq and Coumel (11) showed that the presence of late potentials on signal-averaged ECGs was a very specific marker for the presence of right ventricular dysplasia, although there was no correlation between the presence of late potentials and the extent of right ventricular abnormalities on angiography. Methods for defining right ventricular abnormalities on angiography has not been described owing to a lack of satisfactory criteria. Routine echocardiography is an insensitive tool for detecting early changes in right ventricular dysplasia, but the sensitivity of the technique can be increased by using specific views of the right ventricle (15). This should

Table 3. Correlation Coefficients, p Values and 95% Confidence Intervals for Significant Correlations for Right Ventricular Cavity Dimensions and Signal-Averaged Electrocardiographic Variables

| | RVI | | | RVB | RVOT | | | |
|--------------|-------|-----------|-------------|--------------|-------------|-----------|-------|-------------|
| | 1 | 2 | 3 | | 1 | 2 | 3 | 4 |
| QRSd | | | | | | | | |
| r coeff | 0.50 | 0.44 | 0.72 | 0.89 | 0.70 | 0.49 | 0.45 | 0.23 |
| p value | 0.14 | 0.20 | 0.02 | 0.001 | 0.02 | 0.15 | 0.12 | 0.53 |
| 95% CI | | 0.17-0.93 | | 0.59-0.97 | | 0.13-0.92 | | |
| LPD40 | | | | | | | | |
| r coeff | 0.42 | 0.36 | 0.48 | 0.80 | 0.50 | 0.51 | 0.61 | 0.18 |
| p value | 0.23 | 0.31 | 0.16 | 0.005 | 0.15 | 0.13 | 0.06 | 0.61 |
| 95% CI | | | | 0.17-0.92 | | | | |
| RMS40 | | | | | | | | |
| r coeff | -0.23 | -0.33 | -0.66 | -0.64 | -0.47 | -0.12 | -0.11 | -0.72 |
| p value | 0.52 | 0.34 | 0.04 | 0.04 | 0.16 | 0.74 | 0.76 | 0.02 |
| 95% CI | | 0.05-0.9 | | 0.02-0.90 | | 0.17-0.9 | | |

Statistically significance correlations are shown in boldface. CI = confidence interval; coeff = coefficient; other abbreviations as in Table 2.

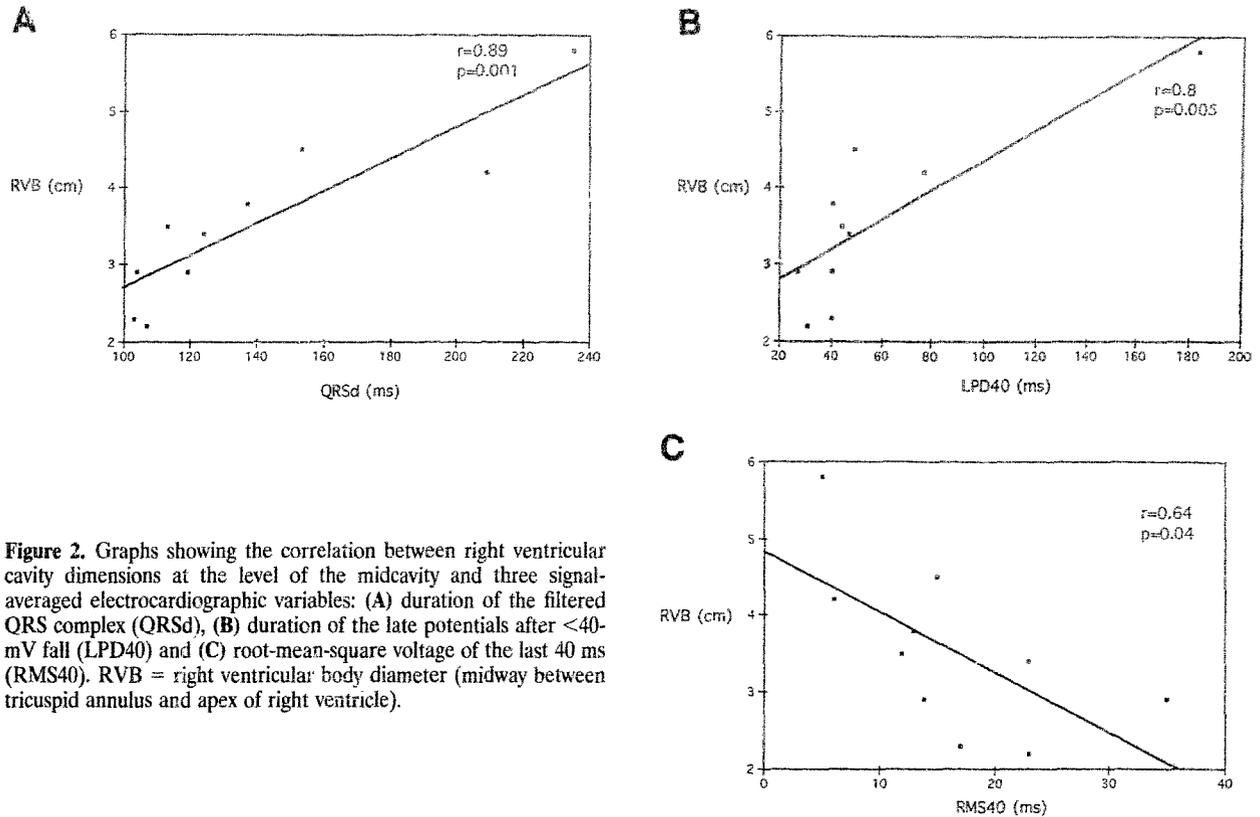


Figure 2. Graphs showing the correlation between right ventricular cavity dimensions at the level of the midcavity and three signal-averaged electrocardiographic variables: (A) duration of the filtered QRS complex (QRSd), (B) duration of the late potentials after <40-mV fall (LPD40) and (C) root-mean-square voltage of the last 40 ms (RMS40). RVB = right ventricular body diameter (midway between tricuspid annulus and apex of right ventricle).

include visualization of the entire right ventricle, because dysplastic changes can start and be localized to the apex, anterior wall or outflow tract (5). Echocardiography, however, has two major limitations. First, a good echocardiographic window is essential for adequate assessment. Second, echocardiography does not appear to be a good tool for detecting adipose tissue in the right ventricular wall. Magnetic resonance imaging has been used for the same purpose. Initial experience indicates that it might be a better tool for early diagnosis, because it can differentiate adipose tissue from muscle (21,22). However, it is expensive, and recent data show that wall thinning and patchy changes of dysplasia might not always be detected by this technique (22). Because of the high cost, limited availability and absence of data in normal control subjects, MRI was not used in the present study.

Value of 12-lead electrocardiography. Routine 12-lead electrocardiography is often abnormal in patients with right ventricular dysplasia, although the changes are not specific. The most frequently reported abnormalities are T wave changes in the precordial leads, which are seen in 90% of patients (4,6,8). Marcus et al. (6) reported prolongation in the QRS duration, which the investigators attributed to a delay in conduction over the right ventricle. Fontaine et al. (7) called these the postexcitation, or epsilon, waves and confirmed their

presence by intracardiac electrograms. These workers reported that a combination of QRS prolongation and T wave inversion provided a sensitivity of 80% and a specificity of 100% in identifying patients with right ventricular dysplasia (8). Electrocardiographic changes, however, were not correlated with the extent of disease. Metzger et al. (4), in a relatively recent study involving 20 patients, found T wave abnormalities and prolongation of the QRS duration to be the most frequent abnormalities. T wave changes were found in 19 patients (95%) and prolongation of the QRS complex in 14 patients (70%). The investigators attempted to correlate the ECG findings with echocardiographic abnormalities; however, there was no correlation between the echocardiographic extent of the disease and ECG findings on 12-lead electrocardiography. Signal-averaged ECGs were not performed in any of the studies just discussed.

Value of signal-averaged electrocardiography. In patients with ventricular tachycardia of right ventricular origin, a normal signal-averaged ECG is indicative of idiopathic ventricular tachycardia, whereas the presence of late potentials points toward underlying cardiac disease such as right ventricular dysplasia or cardiomyopathy (10,11,13). The presence of late potentials has been shown to be a very specific but nonsensitive marker for an underlying myocardial pathologic

process. In a previous study involving patients with no clinical evidence of an underlying cardiac pathologic process and with abnormal right endomyocardial biopsies, signal-averaged ECGs had a specificity of 94% and a sensitivity of 45% (10). In the presence of advanced disease with clinically apparent right ventricular enlargement, signal-averaged ECGs are almost always abnormal (11). However, the quantitative relation between abnormal signal-averaged ECG variables and the degree of right ventricular enlargement has not been previously evaluated.

Correlation between signal-averaged ECGs and right ventricular enlargement. In the present study the QRS duration on routine 12-lead electrocardiography was normal in all patients, indicating that a subset of patients with a milder form of right ventricular disease was included, because in advanced disease patients have either a prolonged QRS duration or right bundle branch block. However, despite a normal QRS duration on 12-lead electrocardiography, QRS duration on signal-averaged electrocardiography was abnormal in 9 of the 11 patients. This could be explained on the basis of the relatively small bulk of the diseased myocardium. Compared with the left ventricular bulk, the proportion of diseased ventricular myocardium that is activated relatively late in right ventricular dysplasia is small, thus the QRS duration on routine 12-lead electrocardiography is not altered. Delayed and slow activation of the right ventricle leads to low amplitude late potentials that may or may not be apparent on the 12-lead ECG but that are amplified by signal averaging. Thus, signal averaging appears to be a useful tool for detecting these low amplitude, delayed signals generated by a relatively smaller bulk of diseased right ventricular myocardium. Furthermore, this study shows that there was a significant correlation between the duration of the filtered QRS complex and the size of the right ventricle. With the enlargement of the right ventricle, it seems probable that there are areas of right ventricular myocardium that are activated late, leading to dispersion of depolarization. The extent of dispersion of depolarization, as expected, would be related to the enlargement of the right ventricular cavity. The delayed activation could be related to the longer time taken by the impulse to capture the enlarged right ventricle or the delayed conduction in the adipose and fibrous tissues that replace muscle in right ventricular dysplasia (10,23,24). The latter mechanism seems to be more likely, as has been suggested in studies involving a comparison of cardiac mapping and 12-lead ECGs (24).

The absence of a correlation between the inflow and the outflow tract with signal-averaged ECG variables is probably due to less involvement of these areas in early or milder forms of right ventricular dysplasia, as these portions of the right ventricle have less myocardium and more fibrous tissue. In addition, the apical four-chamber view is the most reproducible of the echocardiographic measurements used. This view facilitates measurements of the true midcavity, which is probably affected early in the course of the disease, as compared with the right ventricular inflow and outflow tracts.

Conclusion. The majority of patients with "early" right ventricular dysplasia have abnormal signal-averaged ECGs, as defined by standard criteria. Although all three variables measured at signal-averaged electrocardiography correlate with the extent of right ventricular enlargement at the level of the right ventricular midcavity, the duration of the filtered QRS complex is the most useful variable to measure the extent of right ventricular enlargement. There is no consistent correlation between the signal-averaged ECG variables and the changes in the right ventricular dimensions at the level of the outflow and inflow tracts of the right ventricle.

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