New Quantitative Criteria of Time-Domain Signal-Averaged Electrocardiogram in Patients with Bundle Branch Block: Evaluation in Arrhythmogenic Right Ventricular Cardiomyopathy

Katsuya Kajimoto, Kanki Inoue, Hiroshi Kasanuki

From Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan

Address for Correspondence: Katsuya Kajimoto, M.D., Department of Cardiology, Tokyo Women's Medical University, 8-1, Kawada-cho, Shinjuku-ku, , Tokyo, 162-8666, Japan, Fax: +81-3-3356-0441; E-mail: katsuyakajimoto@aol.com

Abstract

Background：It is difficult to distinguish between idiopathic right ventricular tachycardia (IRVT) and arrhythmogenic right ventricular cardiomyopathy (ARVC). Although the use of signal-averaged electrocardiogram (ECG) to diagnose ARVC is known, the occurrence of complete bundle branch block (BBB) in patients with ARVC is frequent. In these conditions with an enhanced QRS duration, the normal values usually adopted are not applicable, and the interpretation of the results is more difficult. Therefore, in order to differentiate patients with IRVT and ARVC by signal-averaged ECG despite BBB, we evaluated the two signal-averaged ECG parameters quantitatively: root mean square voltage for the last 40ms (RMS40) and a ratio of the duration of low amplitude signal <40μV to total filtered QRS duration (LAS40/f-QRS ratio).

Methods: Eighty-four patients with right ventricular tachycardia were investigated by time-domain SAECG. In 42 patients without BBB (IRVT= 23 pts, ARVC=19 pts) and 42 patients with BBB (IRVT= 10 pts, ARVC=32 pts), the values of the two variables (RMS40 and LAS40/f-QRS ratio) were analyzed. Then, we retrospectively investigated the efficacy of new combination criteria (RMS40<20μV and LAS40/f-QRS ratio>0.34) for differentiating patients with IRVT and ARVC by signal-averaged ECG despite BBB.

Results: 1) Among 42 patients without BBB, the combination criteria of RMS40<20μV and LAS40/f-QRS ratio>0.34 distinguished the ARVC patients with a sensitivity of 89%, a specificity of 83%, a positive predictive value (PV) of 81%, and a negative PV of 90%. 2) In 42 patients with BBB, this combination criterion distinguished the ARVC patients with a sensitivity of 94%, a specificity of 80%, a positive predictive value of 94%, and a negative PV of 80%. 3) In all 84 patients, this combination criterion distinguished the ARVC patients with a sensitivity of 92%, a specificity of 82%, a positive predictive value of 89%, and a negative PV of 87%.

Conclusions: This new criteria of combined RMS40<20 μV and ratio of LAS40 to filtered-QRS>0.34 showed effective in identifying ARVC patients among right ventricular tachycardia despite BBB.

Therefore, a diagnosis of ARVC can be made reliably on the basis of clinical presentation, imaging techniques, and this quantitative analysis of signal-averaged ECG. Further studies will be needed to determine if this new combination criteria of RMS40<20 μV and ratio of LAS40 to filtered-QRS>0.34 can identify patients with the earlier form or "concealed" phase of ARVC among right ventricular tachycardia despite the presence of bundle branch block.

Introduction

Arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVC) is a heart muscle disease, often familial, that is characterized by structural and functional abnormalities of the right ventricle (RV) due to replacement of the myocardium by fatty and fibrosis tissue. [1-5] The clinical presentation of ARVD/C usually consists of arrhythmias of RV origin ranging from premature ventricular beats to sustained ventricular tachycardia or ventricular fibrillation leading to sudden death. [1-8] A clinical profile of patients with this condition was the first published in 1982 by Marcus et al. [1] Since then, it has been diagnosed with increasing frequency and has been reported to account for 3% to 5% of unexplained sudden death under the age of 65 years. [9, 10] Moreover, evidence of the disease is found in 30% to 50% of family members who are studied by non-invasive tests, including ECG, echocardiography, and signal-averaged ECG.[11, 12] However, until now, there is no clear regarding clinical diagnosis, natural history, risk stratification, outcome, efficacy of antiarrhythmic agents, prophylaxis of life-threatening ventricular arrhythmias, prevention of death, and genetics in patients with ARVD/C.

The major condition which needs to be differentiated from ARVC is an idiopathic ventricular tachycardia arising from the outflow tract of RV. However, it is difficult to distinguish between idiopathic right ventricular tachycardia (IRVT) and ARVC. Although the use of signal-averaged electrocardiography (ECG) to diagnose ARVC is well known, the occurrence of bundle branch block

in patients with ARVC is frequent. In these conditions, with an enhanced QRS duration, the normal values usually adapted are not applicable, and the interpretation of the results becomes difficult[13]. Several criteria of signal-averaged ECG in patients with complete bundle branch block due to myocardial infarction or dilated cardiomyopathy were reported and these predictive values showed only around 50 to 70% by changing the late potential cutoff value.[14, 15] Thus, the criteria for evaluation of patients with complete bundle branch block have not yet been established.

Therefore, in this study, in order to differentiate patients with IRVT and ARVC by signal-averaged ECG despite complete bundle branch block (BBB), we evaluated the two signal-averaged ECG parameters quantitatively: root mean square voltage for the last 40ms (RMS40) and a ratio of the duration of low amplitude signal <40μV to total filtered QRS duration (LAS40/filtered-QRS ratio). [16]

Methods

Study Population

The study was conducted at the Tokyo Women's Medical University, Tokyo, Japan, between January 1991 and December 1998; it included 51 consecutive patients with ARVC and 33 consecutive patients with IRVT.

The diagnosis of ARVC was established on the basis of the criteria proposed by the ARVC task force of the European Society of Cardiology [17].

In 33 patients with IRVT, the findings of all diagnostic tests including 12-lead ECG, echocardiography, chest CT, and left and right ventricular angiography were normal. Furthermore, all 33 patients had undergone radiofrequency catheter ablation for VT arising from RV outflow tract, and all patients with a diagnosis of IRVT had neither recurrence of VT nor progression to ARVC for at least 5 years follow-up period.

The clinical characteristics of the patients with ARVC and IRVT are shown in Table-1.

TABLE 1. Clinical Characteristics

	ARVC (n=51)	IRVT (n=33)
Mean Age	52.3±14.8 y.o.	42.6±13.7 y.o.
Male / Female	43 pts / 8 pts	14 pts / 19 pts
Mean LVEF	56.3±12.2 %	57.5±6.9 %
Mean RVEF	28.0±10.0 %	50.7±9.8 %
Sustained VT	47 pts (92.2%)	14 pts (42.4%)
RBBB	32 pts (62.7%)	10 pts (30.3%)

LVEF; left ventricular ejection fraction, RVEF; right ventricular ejection fraction
VT; ventricular tachycardia, RBBB : Complete Right Bundle branch block

Signal-averaged ECG

Time-domain signal-averaged ECG was recorded with Predictor (Arrhythmia Research Technology) before an administration of antiarrhythmic agents in all cases. A high resolution ECG with high-gain amplification and bidirectional filters (40-300 Hz) was used for signal averaging to record orthogonal X, Y and Z leads. The three filtered signals were then combined into a vector magnitude $(X^2+Y^2+Z^2)^{1/2}$. The noise level was 0.4μV in all cases. The mean values of the four signal-averaged electrocardiographic variables, the duration of the total filtered-QRS (filtered-QRS), the duration of low-amplitude signal<40μV (LAS40), the root mean square voltage for the last 40ms (RMS40) and a ratio of LAS40 to filtered-QRS, were analyzed in 42 patients without complete bundle branch block (IRVT; 23 pts, ARVC; 19 pts) and 42 patients with complete bundle branch block (IRVT;

10 pts, ARVC; 32 pts).

To differentiate patients with IRVT and ARVC by signal-averaged ECG whether patients have complete bundle branch block or not, we evaluated the two signal-averaged ECG parameters quantitatively: root mean square voltage for the last 40ms (RMS40 < 20 μV) and a ratio of the duration of low amplitude signal <40μV to total filtered QRS duration (LAS40 / f-QRS ratio > 0.34) [16]. We came up with 0.34 for a ratio of LAS40 to filtered-QRS dividing 38 by 114, using these standard values.

Statistical Analysis

Data are presented as mean ± SD. To compare signal-averaged ECG parameters in patients with ARVC and in IRVT, the unpaired t test was selected. A probability of $P<0.05$ was considered significant.

Results

The study population comprised of 84 patients (68% were male).

Table-1summarizes the clinical characteristics of IRVT (n=33) and ARVC (n=51) patients.

Signal-averaged Electrocardiographic Data

Figure-1 shows representative signal-averaged ECG resulting from IRVT patients with (panel B) or without bundle branch block (panel A) and ARVC patients with (panel D) or without bundle branch block (panel C).

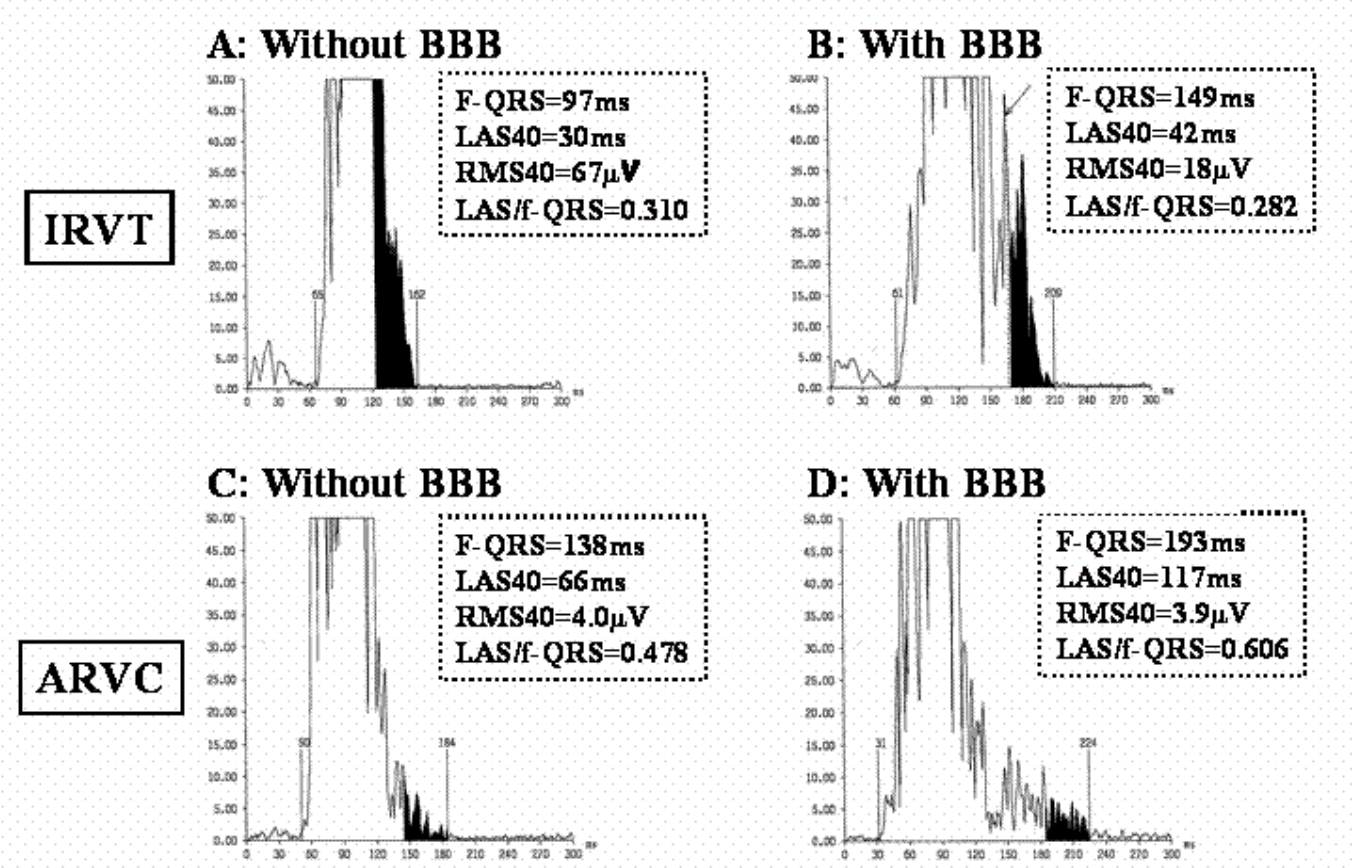

Figure 1. Signal-averaged ECG parameters in IRVT with (panel B) or without BBB (panel A) and in ARVC with (panel D) or without BBB (panel C)

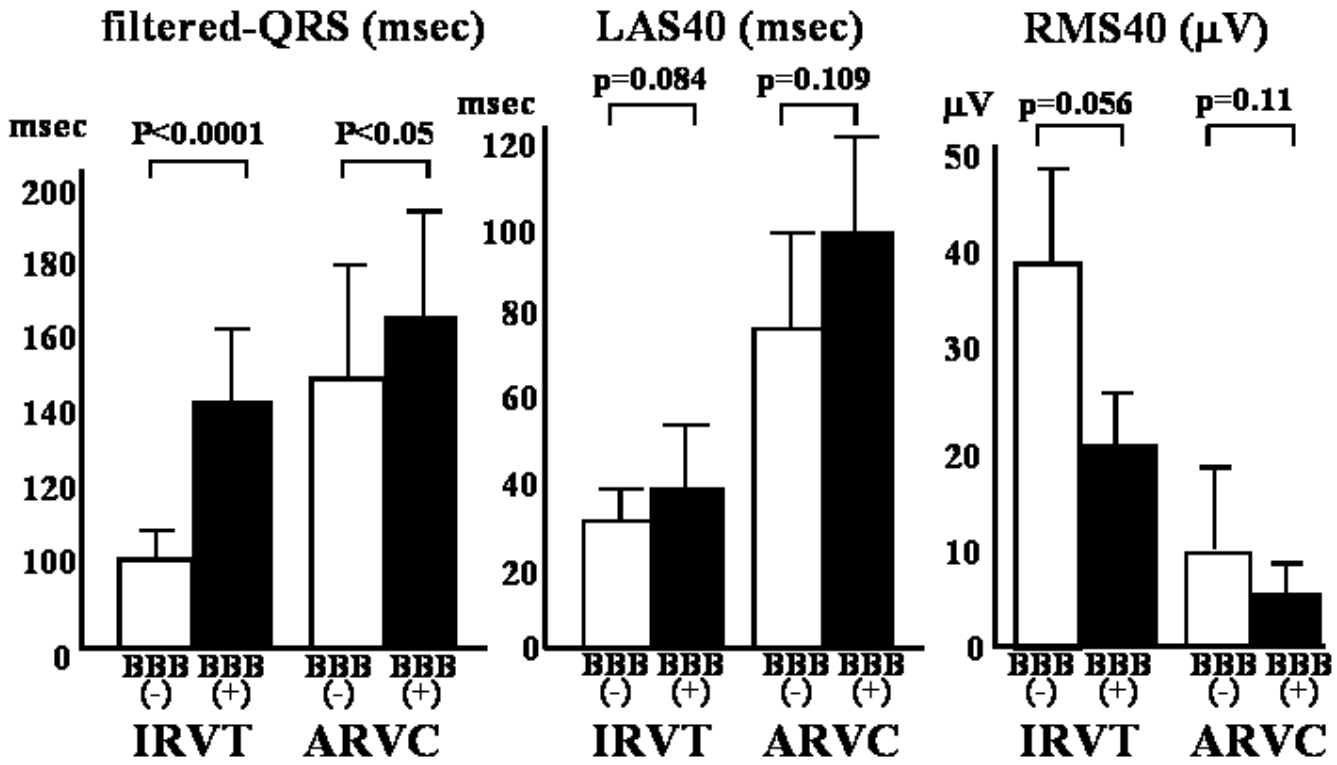

Figure 2. Mean and SD of f-QRS (left), LAS40 (middle), and RMS40 (right) in IRVT and ARVC patients with or without bundle branch block

Figure-2 shows bar graph of filtered-QRS, LAS40, RMS40 in all 33 IRVT patients and all 51 ARVC patients, categorizing if patients had bundle branch block or not. The filtered-QRS was significantly wider in both groups with bundle branch block (figure 2, left panel). There was no significant difference in LAS40, but there was a tendency that the LAS40 prolong with bundle branch block in the ARVC group (figure 2, middle panel). RMS40 in the IRVT group was 39±10 μV in patients without bundle branch block, whereas it was 20±8 μV in patients with bundle branch block, which had no significant difference. However, this did show a tendency of a 50% decrease. ARVC was 9.7±7.2 μV in patients without bundle branch block and 5.2±3.3 μV in patients with bundle branch block, which tended to decrease as well (figure 2, right panel).

On the other hands, the ratio of LAS40 to filtered-QRS showed almost equivalent value for both IRVT

and ARVC regardless if there was bundle branch block or not (figure-3).

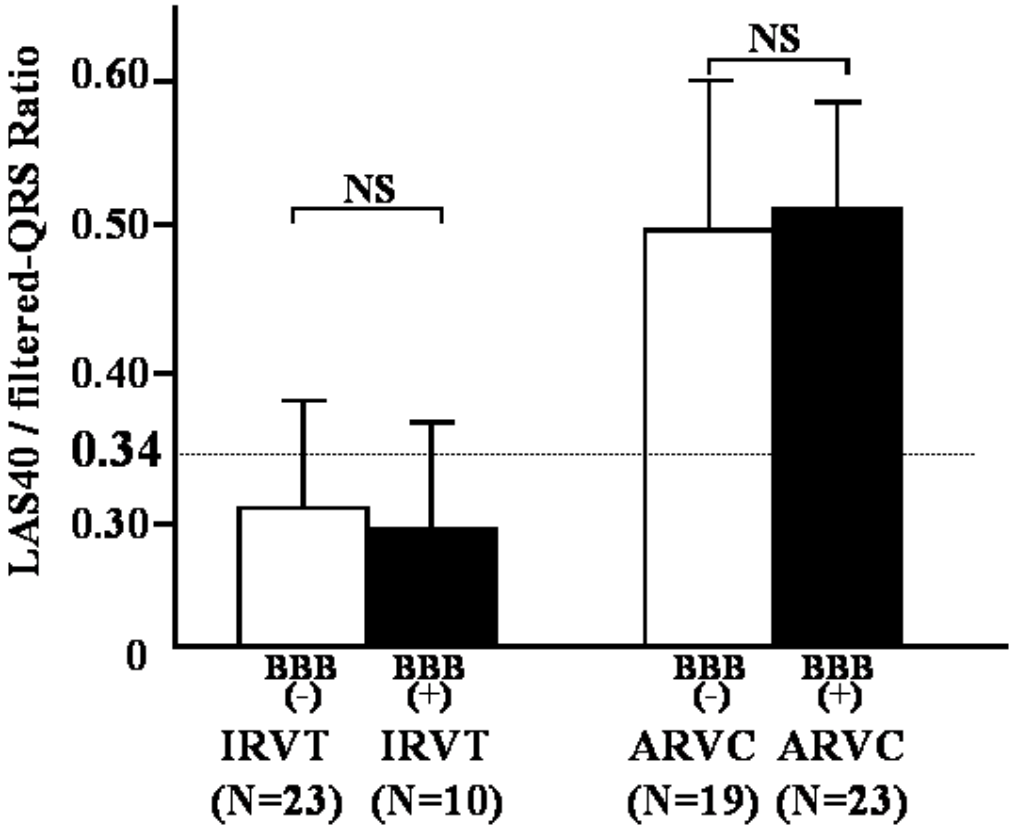

Figure 3. Mean and SD of the ratio of LAS40 to filtered QRS in IRVT and ARVC patients with or without bundle branch block

In Figure 4, we evaluated whether f-QRS duration had a correlation with RMS40 and with LAS40 in 33 patients with IRVT (panel A and B) and in 51 patients with ARVC (panel C and D). The filtered-QRS duration had no significant positive correlation with RMS40 in patients with IRVT and ARVC. Further, there was a weak positive correlation between the filtered-QRS duration and LAS40 in patients with IRVT (R = 0.531, R^2= 0.282、p<0.05). In contrast, in patients with ARVC, there was a strong positive correlation between the filtered-QRS duration and LAS40 (R = 0.903, R^2= 0.816, p<0.0001).

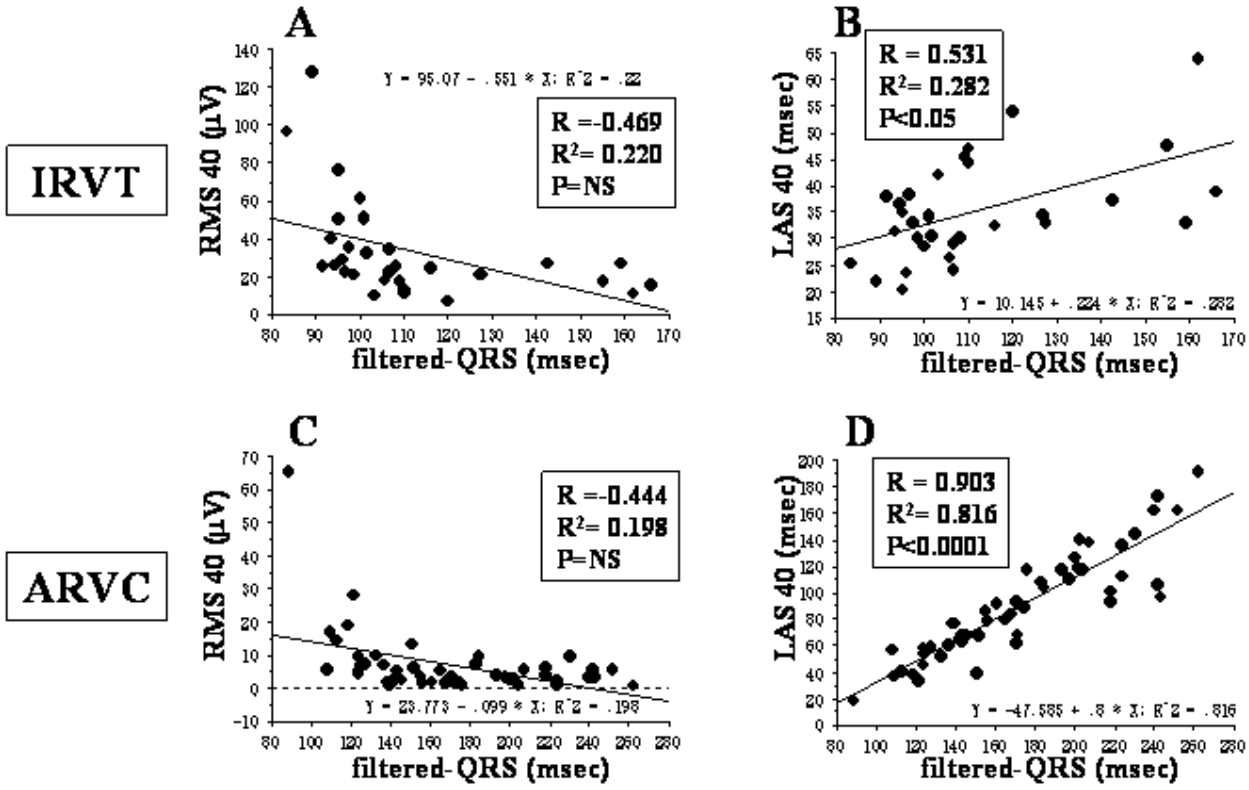

Figure 4. Correlation filtered-QRS duration with RMS40 and with LAS40 in 33 patients with IRVT (panel A and B) and in 51 patients with ARVC (panel C and D)

The distribution of values of the RMS40 and ratio of LAS40 to filtered-QRS in 42 patients without bundle branch block are shown in Figure 5. RMS40 was 9.7±8.2 μV and 38.9±21.2 μV for ARVC and IRVT, respectively, and it showed lower value for ARVC with significant difference. The ratio of LAS40 to filtered-QRS was 0.487±0.123 and 0.328±0.086 for ARVC and IRVT, respectively, and this ratio showed higher value for ARVC with significant difference.

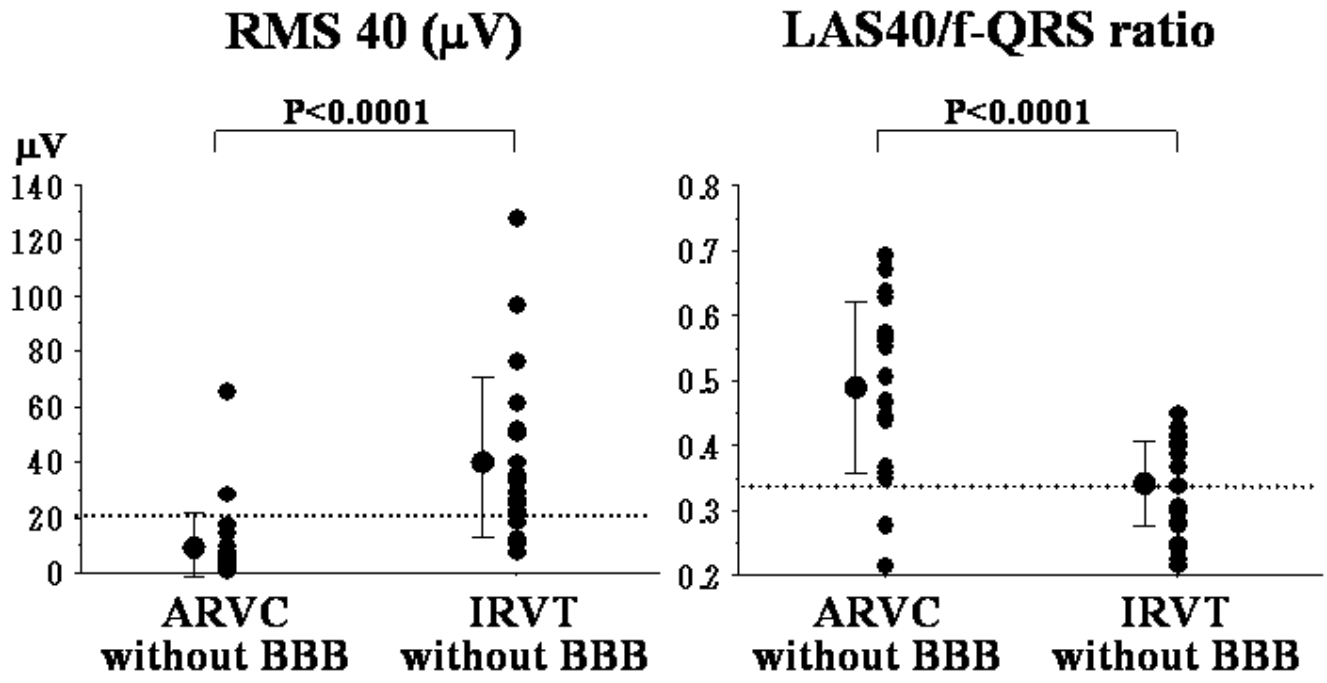

Figure 5. Plots of the RMS40 (left) and ratio of LAS40 to f-QRS (right) in IRVT and ARVC patients without bundle branch block. Dotted line shows a cut-off value for predictors.

The distribution of values of the RMS40 and ratio of LAS40 to filtered-QRS in 42 patients with bundle branch block are shown in Figure 6. RMS40 was 5.2±4.6 μV and 20.2±4.1 μV for ARVC and IRVT, respectively, and it showed lower value for ARVC with significant difference. The ratio of LAS40 to filtered-QRS was 0.512±0.113 and 0.280±0.076 for ARVC and IRVT, respectively, and this ratio showed higher value for ARVC with significant difference.

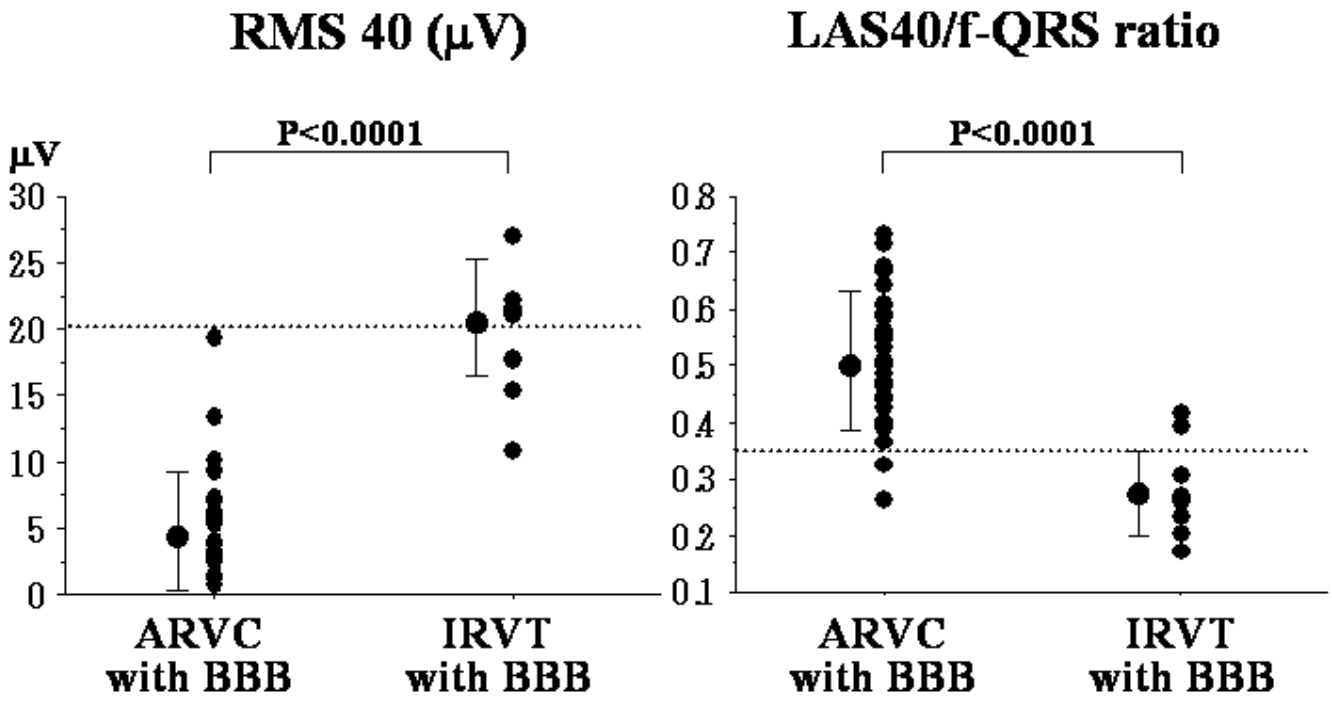

Figure 6. Plots of the RMS40 (left) and ratio of LAS40 to f-QRS (right) in IRVT and ARVC patients with bundle branch block. Dotted line shows a cut-off value for predictors.

The distribution of values of the RMS40 and ratio of LAS40 to filtered-QRS in all 84 patients are shown in Figure 7. RMS40 was 6.9±6.3 μV and 33.2±18.3 μV for ARVC and IRVT, respectively, and it showed lower value for ARVC with significant difference. The ratio of LAS40 to filtered-QRS was 0.502±0.137 and 0.314±0.085 for ARVC and IRVT, respectively, and the ratio showed higher value for ARVC with significant difference.

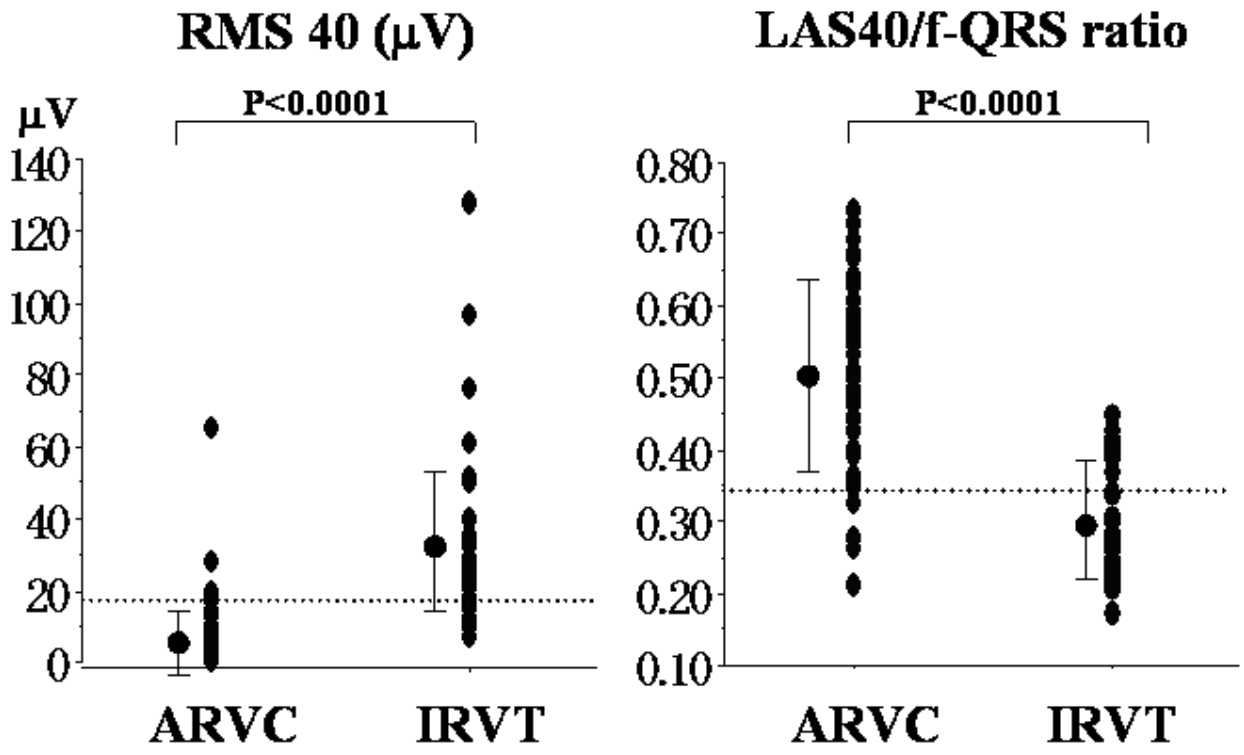

Figure 7. Plots of the RMS40 (left) and ratio of LAS40 to f-QRS (right) in all IRVT and all ARVC patients.
Dotted line shows a cut-off value for predictors.

Diagnostic Value of Time-domain Signal-averaged ECG

The predictive values from 42 patients without bundle branch block who have VT originating from right ventricle are shown in Table 2 (upper panel). Among these 42 patients without BBB, the combination criteria of RMS40<20μV and LAS40/f-QRS ratio>0.34 distinguished the ARVC patients with a sensitivity of 89%, a specificity of 83%, a positive predictive value of 81%, and a negative predictive value of 90%.

The predictive values from 42 patients with bundle branch block who have VT originating from right ventricle are shown in Table 2 (middle panel). In these 42 patients with BBB, this combination criterion distinguished the ARVC patients with a sensitivity of 94%, a specificity of 80%, a positive predictive value of 94%, and a negative predictive value of 80%.

The predictive values from all 84 patients who have VT originating from right ventricle are shown in Table 2 (lower panel). Regardless if there was bundle branch block or not, in all 84 patients, this combination criterion distinguished the ARVC patients with a sensitivity of 92%, a specificity of 82%, a positive predictive value of 89%, and a negative predictive value of 87%.

TABLE 2. Results of Criteria Analysis

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Without BBB (42 patients)				
RMS40<20μV	89%	78%	77%	90%
LAS40/fQRS ratio>0.34	89%	61%	65%	88%
RMS40 < 20μV and LAS40/fQRS > 0.34	89%	83%	81%	90%
With BBB (42 patients)				
RMS40<20μV	100%	60%	89%	100%
LAS40/fQRS ratio>0.34	94%	80%	94%	80%
RMS40 < 20μV and LAS40/fQRS > 0.34	94%	80%	94%	80%
All patients (84 patients)				
RMS40<20μV	96%	73%	84%	92%
LAS40/fQRS ratio>0.34	92%	67%	81%	85%
RMS40 < 20μV and LAS40/fQRS > 0.34	92%	82%	89%	87%

Discussions

The results of this study demonstrate the new signal-averaged ECG parameter, the ratio of LAS40 to filtered-QRS, was effective for identifying ARVC patients among right ventricular tachycardia despite the presence of bundle branch block. Furthermore, it is suggested that it gave better predictive values when combined the ratio of LAS40 to filtered-QRS with RMS40.

The ACC/AHA Task Force has recommended that signal-averaged ECG be considered abnormal if two or more of the following are present: f-QRS≥114ms, LAS40≥38ms, and

RMS40<20μV.[18] This conventional criteria has been extensively based on results obtained from post-myocardial infarction with ventricular arrhythmias. Therefore, until now, it has been reported that the application of this method in patients with ARVC, considering the very different anatomical alterations in comparison with subjects with post-myocardial infarction, made the use of different standard values necessary. Furthermore, in patients with an enhanced QRS duration such as bundle branch block, it is suggested that these standard values are not applicable and the interpretation of the results is more difficult. In patients with bundle branch block due to myocardial infarction or dilated cardiomyopathy, these predictive values showed only around 50 to 70% by changing the late potential cutoff value.[14, 15] Thus, the criteria for evaluation of patients with bundle branch block have not yet been established.

In the present study, in order to differentiate patients with IRVT and ARVC by signal-averaged ECG whether patients have complete bundle branch block or not, we evaluated the two signal-averaged ECG parameters quantitatively: RMS40<20 μV and the ratio of LAS40 to filtered-QRS (LAS40/f-QRS ratio>0.34) [16] whose cutoff values are standard values. This new combination criteria of RMS40<20 μV and the ratio of LAS40 to filtered-QRS>0.34 distinguished the ARVC patients with a sensitivity of 92%, specificity of 82%, positive predictive value of 89%, and negative predictive value of 87% (Table 2). Thus, these results suggest that this criteria using standard cutoff values on signal-averaged ECG is effective in identifying ARVC patients among right ventricular tachycardia despite the presence of bundle branch block.

In order to assess why a new signal-averaged ECG parameter, the ratio of LAS40 to filtered-QRS, was effective in identifying ARVC patients among right ventricular tachycardia despite the presence of bundle branch block, we evaluated whether the f-QRS duration had a correlation with RMS40 and with LAS40 in patients with IRVT and ARVC (figure 4). Although the f-QRS duration had no significant positive correlation with RMS40 in IRVT and ARVC and there was a weak positive correlation between the f-QRS duration and LAS40 in IRVT, there was a strong positive correlation between the

f-QRS duration and LAS40 in ARVC. Nava et al[19] has shown that there was a closer correlation between the signal-averaged ECG and extent of the right ventricular enlargement in patients with ARVC. Therefore, it is possible to speculate that a long LAS40 duration or a high ratio of LAS40 to filtered-QRS may reflect slow and inhomogeneous condition of a large mass in right ventricle and such right ventricle may be vulnerable to sustained ventricular tachycardia or ventricular fibrillation.

Study Limitations

In this study, we analyzed data retrospectively from 84 patients with a right ventricular arrhythmia referred to our hospital over an eight-year period; these patients had no clinical evidence of structural heart disease other than suspected right ventricular cardiomyopathy. Therefore, this type of patient selection is a limitation of the present study, as most of the patients were referred to our hospital after primary assessment in other institution, so a referral bias must be assumed.

Another limitation is that 92% of our patients with ARVC had documented sustained ventricular tachycardia although only 42% of our patients with IRVT had documented sustained ventricular tachycardia. Therefore, in this present study, we do not evaluate an early identification of patients with early phase of the disease (the earlier form or “concealed” phase of ARVC [20, 21]).

Conclusions

The major finding of this study is that this new combined RMS40<20 μV and ratio of LAS40 to filtered-QRS criteria>0.34 is effective in identifying ARVC patients among right ventricular tachycardia despite the presence of bundle branch block. Therefore, a diagnosis of ARVC can be made reliably on the basis of clinical presentation, imaging techniques, and this quantitative analysis of signal-averaged ECG. Further studies will be needed to determine if this new combination criteria of RMS40<20 μV and ratio of LAS40 to filtered-QRS>0.34 can identify patients with the earlier form or “concealed” phase of ARVC of ARVC among right ventricular tachycardia despite the presence of

bundle branch block.

Acknowledgements

We gratefully acknowledge the expert technical assistance of Eriko Ushikubo, RN, Kazunari Takano, RN, Reiko Ohnishi, RN, and Koichi Takeuchi, RN

References

1. Marcus FI, Fontaine G, Guiraudon G, et al. Right ventricular dysplasia. A report of 24 adult cases. Circulation. 1982;65:384-398
2. Thiene G, Nava A, Corrado D, et al. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med. 1988;318:129-133
3. Basso C, Thiene G, Corrado D, et al. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? Circulation. 1996;94:983-991
4. Corrado D, Basso C, Thiene G, Mckenna WJ, Davies MJ, Fontaliran F, Nava A, Silvestri F, Blomstrom-Lundqvist C, Wlodarska EK, Fontaine G, Camerini F: Spectrum of clonicopathgenic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: A multicenter study. J Am Coll Cadiol.1997;30:1512-1520
5. Marcus FI, Fontaine G: Arrhythmogenic right ventricular dysplasia-cardiomyopathy: A review. PACE. 1995;18:1298-1314
6. Fontine G, Frank R, Tonet JL, et al. Arrhythmogenic right ventricular dysplasia: A clinical model for the study of chronic ventricular tachycardia. Jpn Cir. 1984;48:515-538
7. Rowland E, McKenna WJ, Sugrue D, et al. Ventricular tachycardia of left bundle branch block configuration in patients with isolated right ventricular dilatation. Clinical and electrophysiological features. Br Heart J. 1984;51:15-24
8. Foale RA, Nihoyannopoulos P, McKenna WJ, et al. Right ventricular abnormalities in ventricular tachycardia of right ventricular origin: Relation to electrophysiological abnormalities. Br Heart J. 1986;56:45-54
9. Loire R, Tabib A. Mort subite cardiaque inattendue, bilan de 1000 autopsies. Arch Mal Coeur. 1996;89:13-18
10. Maron BD, Shirani J, Poliac LC, et al. Sudden death in young competitive athletes. JAMA. 1996;276:199-204
11. Nava A, Thiene G, Canciani B, et al. Familial occurrence of right ventricular dysplasia: a study involving neine families. J Am Coll Cadiol. 1988;12:1222-1228
12. Hermida JS, Minassian A, Jarry G, et al. Familial incidence of late ventricular potentials and

electrocardiographic abnormalities in arrhythmogenic right ventricular dysplasia. Am J Cardiol. 1997;79:1375-1380

13. Kinoshita O, Fontaine G, Rosas F, et al. Time- and Frequency-Domain analyses of the signal-averaged ECG in patients with arrhythmogenic right ventricular dysplasia. Circulation. 1995;91:715-721
14. Buckingham TA, Thessen CC, Stevens LL, et al. Effect of conduction defects on the signal-averaged electrocardiographic determination of late potentials. Am J Cardiol. 1988;61:1265-1271
15. Brembilla-perrot B, de la Chaise AT, Jacwuemin L, et al. The signal-averaged electrocardiogram is of limited value in patients with bundle branch block and dilated cardiomyopathy in predicting inducible ventricular tachycardia or death. Am J Cardiol. 1997;79:154-159
16. Blomström-lundqvist C, Hirsch I, Olsson SB, et al. Quantitative analysis of the signal-averaged QRS in patients with arrhythmogenic right ventricular dysplasia. Eur Heart J. 1988;9:301-312
17. McKenna WJ, Thiene G, nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Diesease of the European Society of Cardiology and of the Scientific council on cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J. 1994;71:215-218
18. ACC Expert Consensus document on signal averaged electrocardiography. J Am Coll Cardiol. 1996;27:238-249
19. Thiene G, Nava A, Corrado D, et al. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med. 1988;318:129-133
20. Nava A, Folino AF, Bauce B, et al. Signal-averaged electrocardiogram in patients with arrhythmogenic right ventricular cardiomyopathy and ventricular arrhythmias. Eur Heart J. 2000;21:58-65
21. Nasir KN, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity. A need to broaden diagnostic criteria. Circulaion. 2004;110:1527-1534