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Long-term follow-up of the signal-averaged ECG in arrhythmogenic right ventricular cardiomyopathy: correlation with arrhythmic events and echocardiographic findings

Antonio Franco Folino*, **Barbara Bauce**, **Gianfranco Frigo**, and **Andrea Nava**

Department of Cardiology, University of Padua, Padua, Italy

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Aims The aims of our study were to evaluate late potential changes during long-term follow-up in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and to correlate these results with echocardiographic findings and sustained ventricular tachycardia (VT) occurrence.
Methods and results We studied 31 patients (22 males and 9 females; mean age 29 ± 16) during 8 years of follow-up by signal-averaged ECG (SAECG) and echocardiography. Ten subjects experienced episodes of sustained VT. During follow-up, all the SAECG parameters showed a progressive significant increase in late potentials. In contrast, echocardiographic indices did not show evidence of relevant modifications. Patients with sustained VT were characterized by significantly lower left and right ventricular ejection fractions, longer values of filtered QRS at 25/40/80–250 Hz filters, and longer high-frequency low-amplitude (HFLA) signals at 25–250 Hz at baseline. The analysis of SAECG modification during follow-up indicated that only HFLA signals at 25–250 Hz increased significantly in the sustained VT group.
Conclusion We detected a progressive increase in delayed ventricular conduction by SAECG not associated with significant echocardiographic changes. Therefore, the conduction disturbance seems to increase independently from anatomical alterations. The baseline SAECG and echocardiographic parameters, more than their modifications during follow-up, appear to be useful in identifying patients with sustained VT.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a myocardial disease characterized by fibro-fatty substitution of the right ventricle.[1,2] A familial occurrence is well-recognized,[3] and the genetic origin of the cardiomyopathy was demonstrated in several studies.[4–6] All the right ventricular free walls can be involved in the degenerative process, but more frequently, the lesions are localized in the right ventricular inflow, apex, and infundibulum. The pathological alterations can be localized, but we can frequently observe a progressive extension of the disease, with left ventricular involvement.

The myocardial alteration can cause delayed activation in the right ventricle, which in some cases can be seen as a potential in the terminal portion of QRS in V1–V3 leads and is defined as an 'epsilon wave'.[7] More frequently, fragmented electrical activity can be detected by signal-averaged ECG (SAECG). Using this technique, we can disclose a delayed wave front generated in the right ventricle, which can be considered a diagnostic sign of ARVC,[8–11] and could reveal the presence of an anatomical substrate potentially responsible for ventricular tachycardia (VT). Signal-averaged ECG was first used to stratify the arrhythmic risk in patients with myocardial infarction, but the application of this method in subjects with ARVC has also shown a significant correlation between presence of late potentials and occurrence of sustained VT.[12,13]

Signal-averaged ECG and echocardiography are, in addition, non-invasive diagnostic tests that can easily be performed during follow-up, providing useful information about the changes in conduction disturbances and disease evolution.

In this study, we compared SAECG and echocardiographic modifications, during a long-term follow-up, in patients with ARVC correlating the results with the occurrence of sustained VT.

* Corresponding author: Department of Cardiology, University of Padua, Via Giustiniani 2, 35128 Padova PD, Italy. Tel: +39 049 8212426; fax: +39 049 8761764.
E-mail address: franco.folino@unipd.it

Patients

We evaluated 31 patients with ARVC (22 males and 9 females) of 39 consecutive subjects that were referred to our centre in the period January–June 1994. Six patients were lost to follow-up as they refused to make subsequent visits. Two patients were excluded from the study because they needed chronic treatment with amiodarone, known to affect intraventricular conduction and, therefore, SAECG. The remaining subjects completed, as requested in our protocol, the 8-year follow-up, with regular examinations every 2 years.

The mean age at baseline was 29 $\pm$ 16 years, ranging from 9 to 68 years. The diagnosis of ARVC was based on the already published criteria.[14–17] On the basis of McKenna's classification, the diagnosis of ARVC is fulfilled by the presence of two major criteria, one major plus two minor criteria, or four minor criteria from different groups (*Table 1*). In our series, five patients showed two major plus three minor criteria; three patients, two major plus two minor criteria; one patient, one major plus four minor criteria; eight patients, one major plus three minor criteria; five patients, one major plus two minor criteria; and nine patients, four minor criteria. The subjects were referred to our centre for ventricular arrhythmias (isolated PVCs, couplets, or triplets; 9 patients), for diagnosis of ARVC in a family member (12 patients), for syncope (2 patients), and for episodes of sustained VT (8 patients). Arrhythmias were noted during Holter monitoring, exercise stress testing, or by standard ECG in the Emergency Room.

After a complete evaluation of the family tree, occurrence of inherited disease was documented in 22 patients (71%). The antiarrhythmic drugs used in the study group were disopyramide, flecainide, and propafenone alone or in association with β-blockers. All patients were instructed to discontinue the drug for an adequate period (four half-lives) before the follow-up visits.

None of the subjects included in the study group had intraventricular conduction disturbances on standard ECG, defined as QRS duration longer than 100 ms, neither at baseline nor during follow-up.

The study was approved by our institutional ethics review board and the patients gave their informed consent.

Methods

Follow-up

The study protocol included outpatient examinations every 2 years until 8 years of follow-up was complete. At each visit, clinical information was collected and the patient underwent echocardiography and SAECG. The subjects were included in the sustained VT group if a VT lasting more than 30 s occurred on standard or ambulatory ECG.

Echocardiographic evaluation

Echocardiogram was performed with a phased-array ultrasound system (Hewlett Packard Sonos 5500, Andover, Massachusetts) with S4 probe for imaging, spectral Doppler, and colour flow mapping. This examination included M-mode, two-dimensional Doppler echocardiography. Parasternal, apical, and subcostal views were stored on Panasonic AG 6200, Secaucus, NJ videotapes that allowed frame-by-frame and real-time playback for detailed evaluation of structure and function. Left ventricular volume was calculated using an ellipsoid biplane area–length model derived from left ventricular images in the apical four-chamber view. The ejection fraction was calculated using the following formula: end-diastolic volume minus end-systolic volume divided by end-diastolic volume. End-diastolic and end-systolic right ventricular volumes were calculated using an area–length method derived from orthogonal planes (apical four-chamber and short-axis subcostal views).[18,19]

The following parameters were considered: left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), right ventricular end-diastolic volume (RVEDV), and right ventricular ejection fraction (RVEF). Normal values for our laboratory, derived for a control group of healthy subjects, are: LVEDV 64 $\pm$ 6 mL/m^2, LVEF 58 $\pm$ 3%, RVEDV 48 $\pm$ 6 mL/m^2, and RVEF 60 $\pm$ 5%.

Signal-averaged ECG

Signal-averaged ECG was performed using a MAC 15 system (Marquette Inc., Milwaukee, IL, USA). The skin was cleaned with ethanol and abraded. The signals were recorded by standard X, Y, Z orthogonal leads and then combined into a vector magnitude, as the result of the square root of the sum of the squares signals of each lead. Time-domain analysis was then obtained using three different band-pass filters at 25–250, 40–250, and 80–250 Hz. An adequate number of beats (ranging from 250 to 400 beats) was analysed to obtain a noise level <0.5 μV. The following parameters for each filter were evaluated: filtered QRS (FQRS) duration, the high-frequency low-amplitude (HFLA) (<40 μV) signal duration, and the root mean square (RMS) of the voltage in the last 40 ms of the FQRS. To avoid arbitrary classifications, the distinction between normal and abnormal SAECG was not made, and the absolute value for each parameter was considered.

Statistical analysis

Variables were tested for normality using the Kolmogorof–Smirnov test and expressed as mean $\pm$ standard deviation. Modifications over time of SAECG and echocardiographic parameters were analysed by within-subjects multivariate analysis of variance (ANOVA) and the differences in modification over time in patients with or without sustained VT were analysed by between-groups multivariate ANOVA. Comparisons of multiple measurements were corrected using Tukey's test. Correlation between two variables was evaluated using linear regression analysis and expressed as the correlation coefficient (r). Statistical significance was assumed with a level of $P < 0.05$.

Results

The results of SAECG and echocardiography at baseline are summarized in *Table 2*. During follow-up, all SAECG parameters showed significant modifications, with a progression of late potentials, expressed by increase in FQRS and HFLA and decrease in RMS. In contrast, echocardiographic indices did not show significant changes (*Figure 1*).

At baseline, RVEDV was significantly correlated with FQRS at 25–250 Hz filter and with HFLA in all filter settings, whereas LVEDV did not show any correlation with SAECG. In comparison with the baseline visit, the subsequent examinations revealed an increasing number of SAECG parameters significantly related to LVEDV and RVEDV. At last visit, RVEDV was significantly related to FQRS and HFLA at all filter settings and to RMS at 25 and 40–250 Hz filters and LVEDV was related to FQRS at all filter settings, to HFLA at 40–250 Hz filter, and to RMS at 40 and 80–250 Hz filters (*Table 3*).

In the eight patients with previous episodes of sustained VT, the therapy was effective in preventing recurrences,

Table 1 Criteria for diagnosis of ARVC

Global and regional dysfunction and structural alteration	
Major	Severe dilatation and reduction of RVEF with no (or only mild) left ventricular impairment. Localized right ventricular aneurysm (akinetic or dyskinetic areas with diastolic bulging). Severe segmental dilatation of the right ventricle
Minor	Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle
	Mild segmental dilatation of the right ventricle
	Regional right ventricular hypokinesia
Tissue characteristics of walls	
Major	Fibro-fatty replacement of myocardium on biopsy
ECG repolarization abnormalities	
Minor	Inverted T-waves on pre-cordial leads (V2 and V3) in people aged more than 12 years and in the absence of right bundle branch block
ECG depolarization/conduction abnormalities	
Major	Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right pre-cordial leads (V1–V3)
Minor	Late potentials seen on SAECG
Arrhythmias	
Minor	Sustained or non-sustained left bundle branch block type VT documented by ECG, Holter monitoring, or during exercise testing. Frequent premature ventricular complexes (>1000/24 h on Holter monitoring)
Family history	
Major	Familial disease confirmed at necropsy or surgery
Minor	Family history of pre-mature sudden death (<35 years) due to suspected arrhythmogenic right ventricular cardiomyopathy
	Family history (clinical diagnosis based on the present criteria)

Table 2 SAECG and echocardiographic parameters at baseline

	Baseline
25–250 Hz	
FQRS (ms)	128.35 ± 14
HFLA (ms)	28.41 ± 13
RMS (μV)	53.9 ± 52
40–250 Hz	
FQRS (ms)	121.22 ± 17
HFLA (ms)	41.48 ± 16
RMS (μV)	26.93 ± 19
80–250 Hz	
FQRS (ms)	109.58 ± 15
HFLA (ms)	40.55 ± 17
RMS (μV)	15.48 ± 15
LVEDV (mL/m^2)	62.8 ± 13
LVEF (%)	60.0 ± 7
RVEDV (mL/m^2)	83.9 ± 23
RVEF (%)	54.7 ± 9

whereas two other subjects showed sustained VT during follow-up. On the whole, the patients with sustained VT did not differ from the other subjects by age (37.7 ± 18 vs. 26 ± 15 years; P = NS) and sex (males: 8/10 vs. 14/21 patients; P = NS). Considering the SAECG parameters at baseline, the patients with sustained VT had more evident late potentials and significantly lower values of LVEF and RVEF (*Table 4*).

The analysis of SAECG modification during follow-up indicated that only HFLA signal at 25–250 Hz increased more significantly in the sustained VT group ($P = 0.010$) (*Figure 2*). The same analysis, considering echocardiographic indices, showed that only LVEDV increased more significantly in sustained VT patients ($P = 0.002$) (*Figure 3*).

Discussion

Re-entry is one of the main mechanisms involved in the genesis of repetitive ventricular arrhythmias in ARVC. It is based on the presence of zones of altered myocardium, characterized by fibro-fatty infiltration, that can create re-entry circuits representing the substrate for repetitive ventricular arrhythmias. Moreover, these anatomical alterations cause a delayed, fragmented activation front, and consequent development of potentials with high-frequency components, which can be detected by SAECG. The use of this method has shown particular reliability in ARVC because of the classical localization of the myocardial alterations in the right ventricle, which induce a delayed potential only in the terminal portion of QRS and, therefore, more easily identifiable by filtering procedures.

In our study, we found significant modifications over time in SAECG parameters, indicating an increase in late potential in patients with ARVC. However, during the 8 years of follow-up, late potentials became more evident but not with a progressive linear increase. Particularly, FQRS and HFLA showed a steady state or a mild decrease in comparison with the previous examination at some visits (*Figure 1*).

This phase of reduction in late potentials is not easy to explain; however, we can make a hypothesis. The progression of the disease with an extension of fibro-fatty degeneration could completely isolate some infiltrated areas, with appearance of different preferential pathways of activation and reduction in late potentials. Additional factors, such as sympathetic activity modulation, could influence SAECG,[20] by modifying the electrophysiological

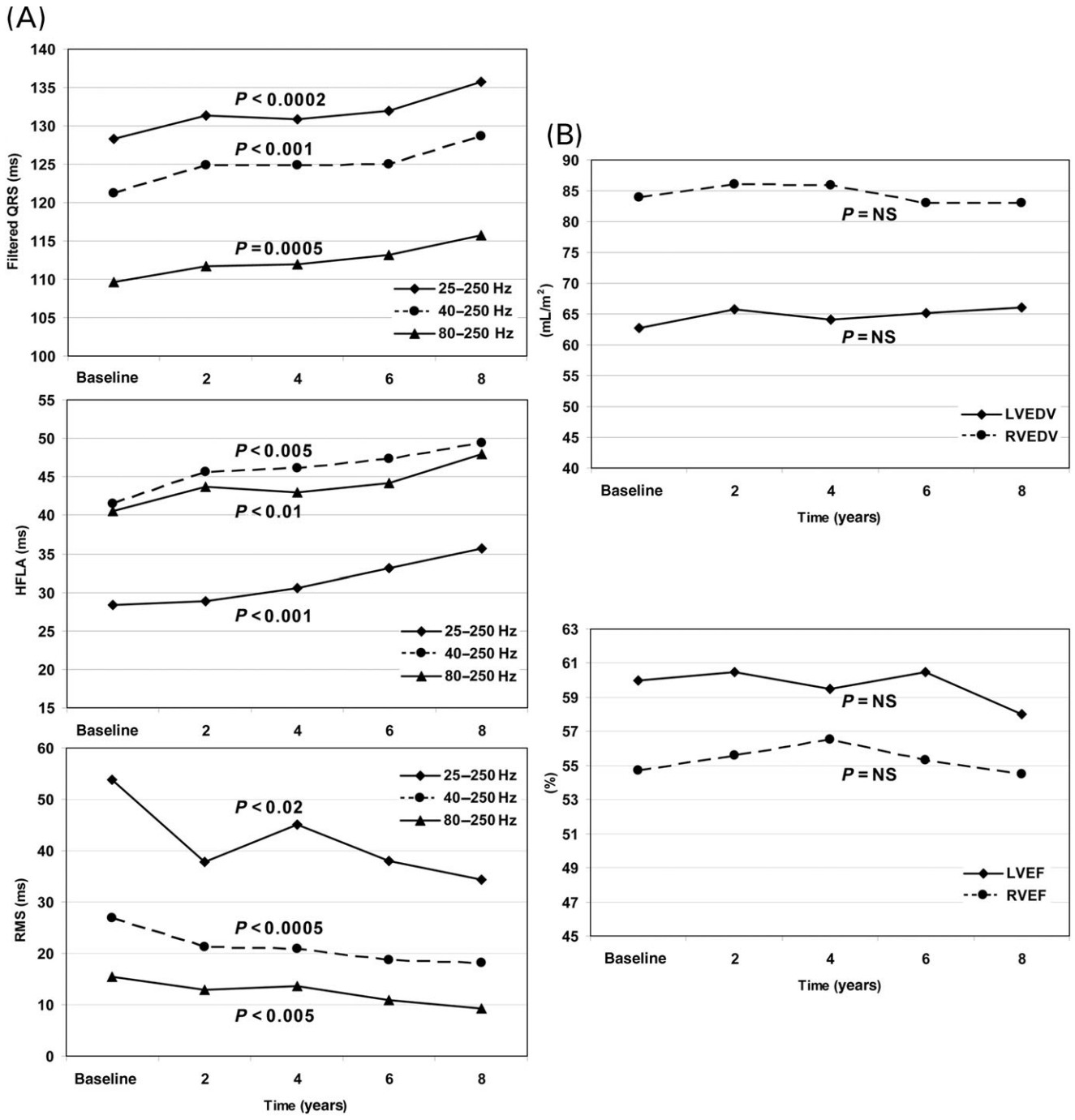

Figure 1 Changes in SAECG (*A*) and echocardiographic parameters (*B*) during 8 years of follow-up. All electrocardiographic parameters showed a significant increase in late potentials, whereas none of the echocardiographic indices showed relevant changes.

properties of the myocardium. Finally, these results could reflect a characteristic process of the disease, with alternate phases of progression and quiescence.[21]

In contrast, echocardiographic indices did not show significant variation during follow-up. To explain this finding, we suppose that when a patient underwent their first evaluation, having been referred to the centre for symptoms or by serendipitous discovery of ECG abnormalities, the disease had already expressed the pathological alterations that induce the modification of right ventricle dimensions and, subsequently, they remain stable over time or with minimal changes. In fact, a recent study that evaluated the progression of the disease in affected families[22] showed a prevalence of the morphological progression of the disease during adolescence. An alternative explanation is that echocardiography could be a technique with a resolution capacity insufficient to detect minimal anatomical modifications.

In our study group, the only parameter with a small, non-significant increase was LVEDV. This is not a usual behaviour in a normal population[23] and should be considered as an extension of the disease to the left side of the heart.

As previously reported by Mehta *et al.*,[24] we found that at baseline, right ventricular dimension was better related to

Table 3 Coefficients of correlation and *P*-values between SAECG and echocardiographic parameters during follow-up

Visit		baseline		2 years		4 years		6 years		8 years	
SAECG		LVEDV	RVEDV	LVEDV	RVEDV	LVEDV	RVEDV	LVEDV	RVEDV	LVEDV	RVEDV
25–250 Hz											
FQRS	*r*	0.1698	0.3666	0.3108	0.4457	0.2546	0.4478	0.3607	0.4468	0.3965	0.4906
	P	NS	<0.05	NS	<0.02	NS	<0.02	<0.05	<0.02	<0.05	=0.001
HFLA	*r*	0.1976	0.5422	0.4262	0.6777	0.1719	0.6004	0.3471	0.6081	0.3298	0.6443
	P	NS	=0.002	<0.02	<0.001	NS	<0.001	NS	<0.001	NS	<0.001
RMS	*r*	0.1632	−0.2001	−0.2987	−0.4681	0.1366	−0.2731	−0.0320	−0.2985	−0.2286	−0.4878
	P	NS	NS	NS	<0.01	NS	NS	NS	NS	NS	=0.001
40–250 Hz											
FQRS	*r*	0.1656	0.3344	0.2786	0.3908	0.3317	0.4321	0.4076	0.5138	0.4388	0.4935
	P	NS	NS	NS	<0.05	<0.05	<0.02	=0.02	<0.005	<0.02	=0.001
HFLA	*r*	0.1757	0.3797	0.2954	0.4250	0.1865	0.5595	0.1676	0.5674	0.4047	0.4500
	P	NS	<0.05	NS	<0.02	NS	=0.001	NS	=0.001	=0.02	=0.001
RMS	*r*	−0.1363	−0.3379	−0.4110	−0.4255	−0.2235	−0.4527	−0.1240	−0.3770	−0.4018	−0.4427
	P	NS	NS	=0.02	<0.02	NS	<0.02	NS	<0.05	=0.02	<0.05
80–250Hz											
FQRS	*r*	0.1071	0.3501	0.2350	0.3978	0.2838	0.4796	0.3792	0.5713	0.4092	0.5220
	P	NS	NS	NS	<0.05	NS	<0.01	<0.05	=0.001	=0.02	=0.002
HFLA	*r*	0.1147	0.4790	0.2160	0.4693	0.2068	0.5401	0.1763	0.5541	0.2492	0.4543
	P	NS	<0.01	NS	<0.01	NS	=0.002	NS	=0.001	NS	=0.001
RMS	*r*	0.1890	−0.2021	−0.0522	−0.2765	0.0536	−0.1961	0.0021	−0.2923	−0.4326	−0.2986
	P	NS	NS	NS	NS	NS	NS	NS	NS	<0.02	NS

Table 4 Comparison of SAECG and echocardiographic indices at baseline, in patients with or without SVT

Variable	No SVT	SVT	*P*-value
25–250 Hz			
FQRS (ms)	124.8 ± 11	135.7 ± 16	<0.05
HFLA (ms)	24.3 ± 10	37.1 ± 13	<0.01
RMS (μV)	63.0 ± 60	34.7 ± 23	NS
40–250 Hz			
FQRS (ms)	116.9 ± 15	130.3 ± 19	<0.05
HFLA (ms)	37.9 ± 14	48.9 ± 19	NS
RMS (μV)	28.8 ± 18	22.9 ± 22	NS
80—250 Hz			
FQRS (ms)	105.4 ± 12	118.4 ± 18	=0.02
HFLA (ms)	37.0 ± 17	47.9 ± 23	NS
RMS (μV)	18.0 ± 17	10.1 ± 8	NS
LVEDV (mL/m^2)	65.8 ± 12	56.5 ± 12	NS
LVEF (%)	61.9 ± 6	55.9 ± 9	<0.05
RVEDV (mL/m^2)	79.6 ± 20	93 ± 26	NS
RVEF (%)	57.4 ± 7	49.2 ± 11	<0.02

SAECG parameters than LVEDV, confirming the importance of the right side localization of the myocardial alterations to generate more evident delayed potentials. However, we assisted in a progressive increase in the number of SAECG parameters significantly related to echocardiographic indices. Considering that heart dimensions did not change significantly over time, we can hypothesize that in the first phases of the disease, the pathological alterations cause an increase in heart volumes. Subsequently, progression of the disease induces only an increase in the fragmented electrical activity, with a corresponding growth of late potentials. In a previous study,[13] we found similar results, showing a significant correlation between SAECG parameters and extension of the disease.

We failed to identify a statistically significant difference in terms of sex and age in patients with and without sustained VT, probably because of the inadequate number of cases. However, a trend seems to identify a higher incidence of the arrhythmia in older male patients.

If we consider the baseline SAECG, it showed that sustained VT patients had more evident late potentials reflected by longer FQRS duration at all filter settings and longer HFLA signal at 25–250 Hz filter. On the contrary, RMS did not reveal significant differences. It is worth noting that the parameter with the best significance was HFLA duration at 25–250 Hz filter, representing the signals with low amplitude. Therefore, high-frequency signals at the larger band-pass filter are more specific signals, indicating the presence of fragmented electrical activity unrelated to a diffuse intraventricular conduction disturbance. Similarly, if we observe SAECG evolution in sustained VT patients, the same index is the only one showing a significantly greater increase in comparison with other subjects.

Moreover, the sustained VT group was identified by lower values of LVEF and RVEF at baseline, but not by right and left ventricular dimensions. It seems that the occurrence of sustained VT is not directly related to the dimension of the heart, but it could be facilitated by an increased sympathetic activity induced by baroreceptor activation, which in turn, is induced by lower cardiac output.

Considering the modifications in echocardiographic findings, we observed that LVEDV was the index showing the most relevant increase during follow-up, even if not statistically significant, in patients with sustained VT. However, it is difficult to establish whether this is a primary effect of the disease or a consequence of the arrhythmias. In contrast, we could imagine that subjects with an extension of the

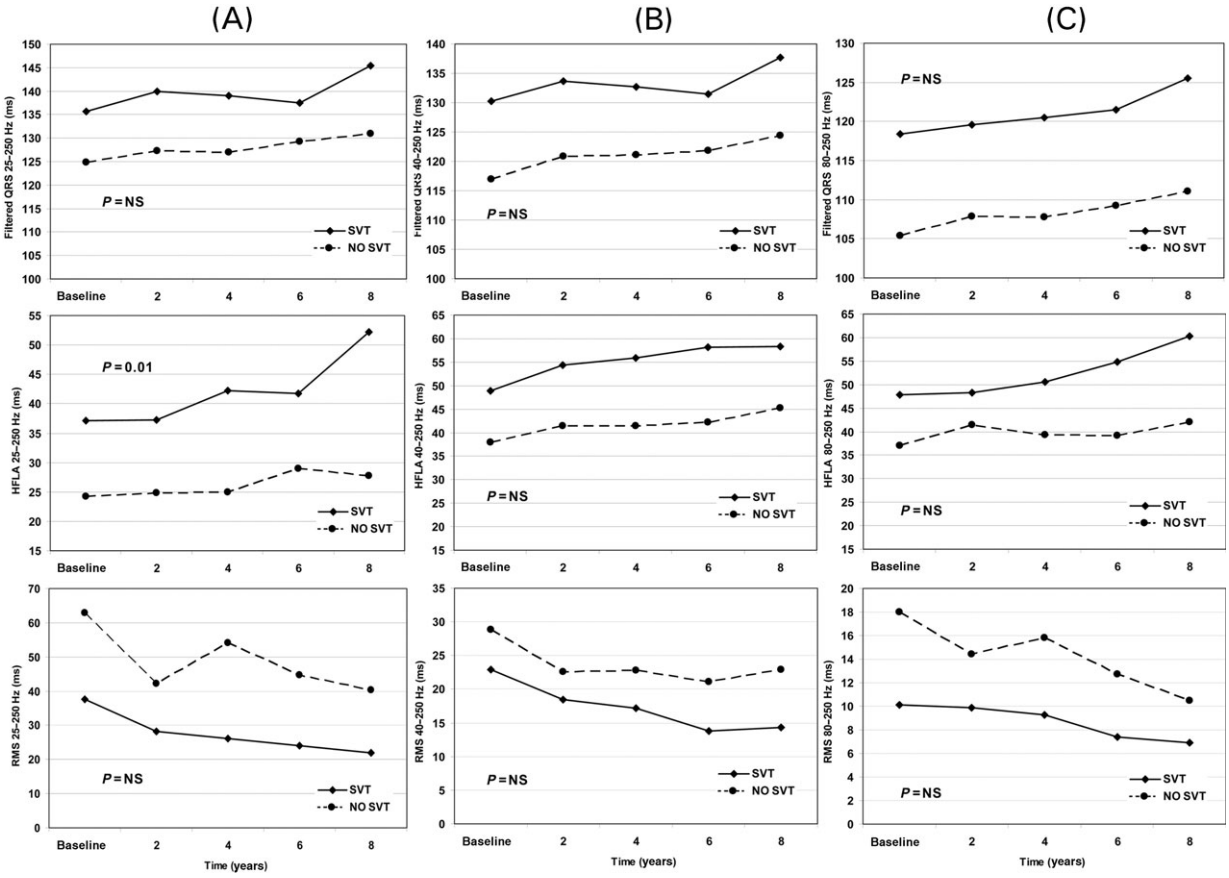

Figure 2 Modifications over time of SAECG at 25–250 Hz (*A*), 40–250 Hz (*B*), and 80–250 Hz (*C*) filters in patients with and without episodes of sustained VT. Only HFLA signal at 25–250 Hz showed a more pronounced increase in patients with sustained VT. *P*, *P*-values in between-group comparisons for repeated measures and SVT, sustained ventricular tachycardia.

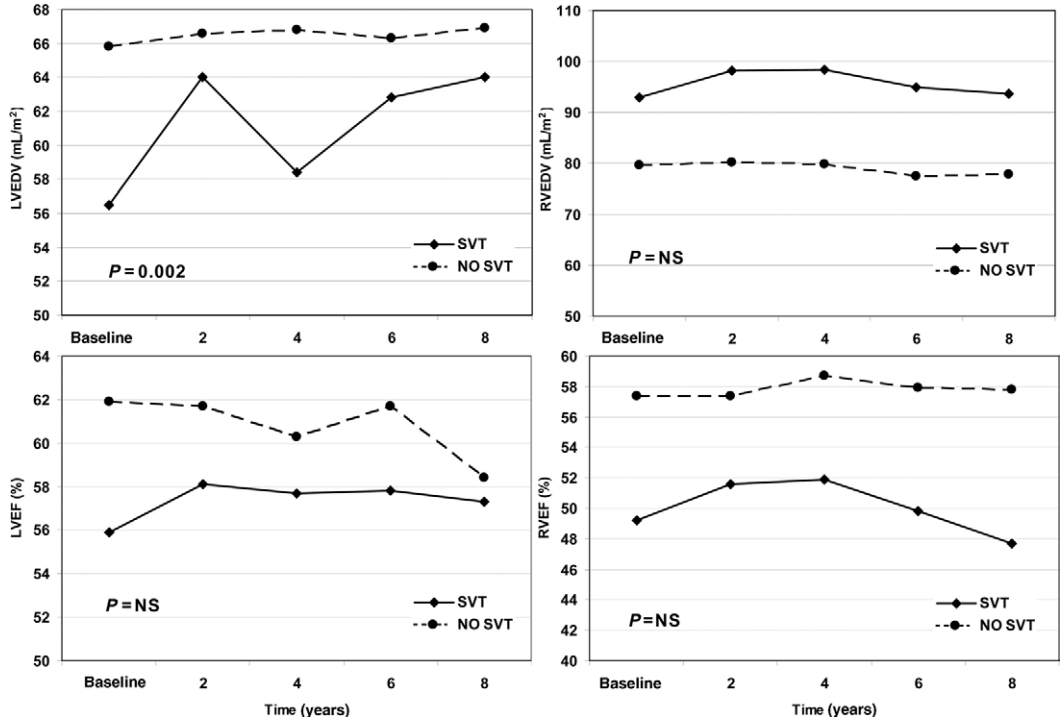

Figure 3 Modifications over time of echocardiographic parameters in patients with and without episodes of sustained VT. LVEDV was the only index that showed a more pronounced increase in patients with sustained VT. *P*, *P*-values in between-group comparisons for repeated measures and SVT, sustained ventricular tachycardia.

disease to the left ventricle could be more prone to develop serious ventricular arrhythmias.

Conclusion

Our study has shown that SAECG can detect a progressive increase in delayed, fragmented depolarization in patients with ARVC in the absence of significant modification in echocardiographic parameters. Therefore, conduction disturbances seem to increase independently of anatomical abnormalities. The presence of late potentials and reduced values of LVEF and RVEF were detected in patients with ARVC and episodes of sustained VT.

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