The Clinical Implications of the Signal-Averaged ECG in Patients with ARVD

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The signal-averaged ECG (SAECG) is now widely used to evaluate the risk of ventricular arrhythmias and sudden death especially in patients with myocardial infarction and cardiomyopathies. Heterogeneous patterns of activation caused by fibrosis are manifested as fragmented, low-amplitude electrograms at the end of the QRS complex, and are called late potentials. Late potentials are considered to be a manifestation of a regional delayed activation of the myocardium and thus serve as a marker for the substrate for reentrant ventricular tachyarrhythmias.

ARVD is characterized by the progressive fatty or fibrofatty infiltration of the myocardium. This pathological abnormality produces 'delayed ventricular potentials' responsible for the late potentials recorded by the SAECG. Late potentials represent a fixed anatomic substrate of reentrant excitation. Usually late potentials are frequent in patients with an extensive form of and documented spontaneous ventricular tachycardia (VT). The SAECG may be used for the diagnosis, family screening of patients and risk stratification of ARVD patients. Unfortunately studies on the SAECG in ARVD patients are rare. The purpose of this review was to gain a better understanding of the role and limitations of the SAECG in patients with ARVD.

Methods and definitions of the SAECG in ARVD

The SAECG requires only QRS complexes with the same morphology for averaging. Selection of the correct QRS complexes is accomplished by an automated template-recognition algorithm and only QRS complexes highly correlated with the templates are averaged. Acquisition can be considerably longer in patients with atrial fibrillation or frequent ectopic beats. Bidirectional digital filters are also used with averaging to reduce noise levels and enhance the identification of the QRS complex. The high-pass filter removes low frequency activity less than 25 or 40 Hz usually associated with the baseline drift of the ECG signal and low frequency component of the ST segment and T wave, enhancing correct identification of the QRS offset. Low-pass filters usually remove high frequencies greater than 250 Hz, such as pectoral muscle potentials.

Time domain analysis is most commonly used to interpret the SAECG. The following parameters are usually evaluated: total filtered QRS duration (fQRS), low amplitude signals <40 uV in the terminal portion of the filtered QRS duration (LAS40) and root mean square of the voltage in the last 40 ms of the filtered QRS (RMS40). A Task Force Committee of the European Society of Cardiology, the American Heart Association and American College of Cardiology recommended that the SAECG should be considered abnormal (using 40-Hz high-pass bidirectional filtering) when 1) the filtered QRS duration is greater than 114 ms, 2) there is a less than 20 uV signal in the last 40 ms of the vector magnitude complex, and 3) the terminal vector magnitude complex remains below 40 uV for more than 38 ms[1)]. Usually the SAECG is considered abnormal when more than two parameters are abnormal. Different criteria for this abnormalitiy have been proposed and they are often

based on using different filters, although relatively few studies have compared the different criteria (Table 1).

Table 1. Definitions of normal parameters in the time-domain analysis of the SAECG and prevalence of late potentials in patients

References	Filter setting	Normal values			Prevalence of LP in patients
		fQRS (M/F)	LAS40	RMS40	
Blomstrom-Lundqvist et al[2)]	25-300 Hz	<120 ms	<40 ms	>25 uV	81%
Leclercq and Coumel[3)]	40-300 Hz	<113 ms	<38 ms	>16 uV	75%
Mehta et al[4)]	25-250 Hz	<120 ms	<40 ms	>25 uV	-
Kinoshita et al[5)]	25-250 Hz	≤120 ms	≤40 ms	≥25 uV	71%
	40-250 Hz	≤114 ms	≤38 ms	≥20 uV	64%
Oselladore et al[6)]	40-250 Hz	<120 ms	<38 ms	>20 uV	-
Hermida et al[7)]	40-250 Hz	≤114 ms	<38 ms	<20 uV	62%
Turrini et al[8)]	40-250 Hz	<122/115 ms	<41 ms	>20 uV	47%
Yoshioka et al[9)]	40-250 Hz	<120 ms	<40 ms	>20 uV	85%
Nava et al[10)] and Nava et al[11)]	25-250 Hz	<120 ms	<40 ms	>25 uV	
	40-250 Hz	<118 ms	<40 ms	>20 uV	
	80-250 Hz	<106 ms	<34 ms	>12 uV	
Hamid et al[12)]	40-250 Hz	≤114 ms	≤38 ms	≥20 uV	58%
Nasir et al[13)]	40-250 Hz	<114 ms	<38 ms	≥20 Uv	45%
O'Donnell et al[14)]	40-250 Hz	<120 ms	≤40 ms	≥20 uV	78%

Another method has been applied to the SAECG to improve the identification of late potentials. Spectral analysis of the SAECG takes advantage of differences in the frequency characteristics between late potentials and the QRS complex and ST segment. This technique can identify the equivalent of 'late potentials' within the QRS complex. A combination of time domain and spectral turbulence analysis of the SAECG was shown to be better than either alone[5)]. Frequent right bundle branch block or intraventricular conduction defects in patients with ARVD have been a significant problem in the time domain analysis of the SAECG. Most studies using time-domain analysis excluded patients with these conditions from further analysis because of the concern for false positive results. As the definition of the end of the QRS complex is not a crucial factor in frequency-domain analysis, patients with these conditions need not be excluded[5)].

The SAECG as a diagnostic tool for ARVD

Late potentials are one of minor diagnostic criteria proposed by the Task Force[15)]. In patients with VT of a right ventricular origin, a normal SAECG is considered as indicative of an 'idiopathic' VT such as RVOT tachycardia, whereas an abnormal SAECG is a specific marker for right ventricular disease, especially ARVD[14)].

The abnormality observed in the SAECG appears to be correlated with the severity or extent of the disease. There were significant correlations between all the SAECG variables and the right ventricular cavity dimensions, right ventricular ejection fraction and extent of myocardial fibrosis on biopsy[4,8,10].

The SAECG does not seem to be useful for diagnosing the minor forms of the disease and does not give precise information about the electrical instability in these patients. However, since it is a noninvasive method, it may be helpful for evaluating the progression of the disease. The SAECG was rarely abnormal in young subjects, but the incidence of abnormal recordings increased progressively with increasing age[6]. This appears to be correlated with an increased percentage of patients with the disease as the age increases (Table 2). For this reason, the diagnosis of patients with minimal disease remains a challenging problem[6,9]. These data support the idea of the progressive nature of the characteristics of ARVD in family members.

Table 2. Values of the SAECG parameters according to the disease extension[6].

	QRSUN*	QRS40	LAS40	RMS40
No heart disease (n=28)	83.7±8.2 ms p<0.001	105.3±6.1 ms p=0.004	24.1±6.2 ms p<0.001	75.2±28.5 uV p<0.001
Minor cardiac involvement (n=31)	96.9±9.9 ms p=0.006	115.7±10 ms p<0.001	32.3±13 ms p<0.001	33.7±26.2 uV p=0.002
Extensive RV disease (n=16)	109.5±20 ms	141±20.5 ms	58.4±17.6 ms	11±7.7 uV

*Unfiltered QRS duration

Optimal high-pass filter settings of the SAECG in patients with ARVD

The mean values of the SAECG parameters were significantly influenced by the high-pass filter setting. High-pass filter settings of 25 to 40 Hz are usually selected. The most widely used high-pass filter setting of 40-Hz is derived from post-MI patients with ventricular arrhythmias in which the high-pass filter set at 40 Hz was considered as the best compromise between the sensitivity and specificity as compared to the 25 and 80 Hz high-pass filter settings[16]. However, patients with ARVD are different from post-MI patients since they have normal or near-normal left ventricles and the VT usually originates from the right ventricle. There are no widely accepted guidelines for the optimal cutoff for an abnormal SAECG in patients with ARVD.

Kinoshita et al[17] reported similar findings in patients with ARVD. As the high-pass filter frequency was increased, there was a decrease in the total filtered QRS duration. The terminal low-amplitude signal duration showed an increase as the high-pass filter frequency was increased. The root-mean-square voltage of the last 40 ms in the normal control group showed a mild decrease. Positive rates decreased as the filtering frequency was increased from 20 to 70 Hz (Figure 1).

Detection of late potentials in ARVD may be improved by employing a high-pass filter of 25 instead of 40-Hz.

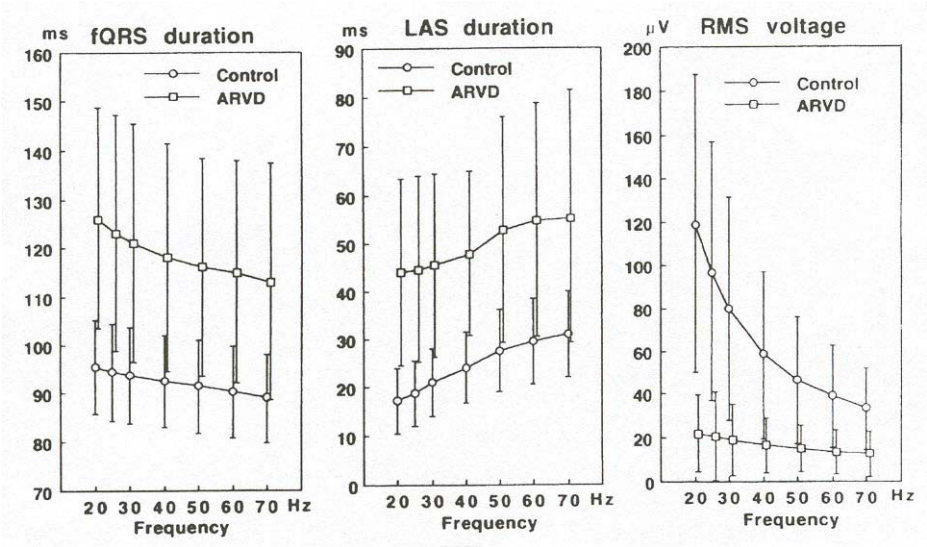

Figure 1. Mean±SD of the SAECG parameters for normal subjects (Control) and for patients with ARVD at 7 high-pass filter settings. The low-pass filter was fixed at 250 Hz[17] .

Risk stratification of sustained VT and sudden death

Most studies showed a close relationship between at least one of the SAECG parameters and the presence of sustained VTs[3,8,10,11,13]. Blomstrom-Lundqvist et al[2] showed a significantly longer LAS40 and lower RMS40 in patients with multiple QRS morphologies during VT than in patients with only one type of VT. Larger areas of electrically, and perhaps even morphologically, abnormal myocardium may be present in the former group.

If the VT originates from an area that is normally activated early, an electrogram of a given duration from this site may not extend beyond the QRS and may thus be concealed. The same theory may also explain the absence of late potentials in patients with RVOT tachycardia. This type of arrhythmia is often present in minor forms of the disease and is difficult to differentiate from idiopathic arrhythmias arising from this area[2,10]. Patients with involvement of the basal areas of the right ventricle, which are the last to be activated, may show well evident late potentials on the SAECG[10].

Not all sudden death or cardiac arrest in patient with ARVD was caused by VT. Patients in an early stage of ARVD with the highest risk of sudden death may not be detected with the SAECG. Some patients with ventricular fibrillation had absolutely normal findings on the SAECG[3]. Absence of late potentials cannot rule out the presence of ARVD or the risk of sudden death. The risk of sudden death is relatively high in the initial stages of ARVD with minor cardiac abnormalities, and the SAECG is more diagnostic in the extensive form, and significant SAECG abnormalities may be considered as a marker of a low risk of sudden death, but as an increased risk of death from heart failure[3].

Family screening

ARVD is a progressive disease appearing during adolescence and early adulthood. Systematic evaluation of family members leads to early identification of ARVD. Family groups represent an ideal study model to evaluate the diagnostic and prognostic value of the SAECG as the transmission of ARVD is autosomal dominant with incomplete penetrance and variable expression[6]. The incidence of late potentials was significantly higher in family members than in normal control subjects[6,7,9,12]. One study reported no significant difference in the incidence of late ventricular potentials in family members according to the initial clinical presentation of the disease, in either familial or sporadic forms, or according to the presence or absence of sudden death in the family[7].

The Task Force Criteria are considered as highly specific but lack sensitivity when evaluating asymptomatic patients and relatives with incomplete expression[12]. Results of some studies suggest that in the setting of a positive family history, even minor abnormalities including positive late potentials may be diagnostic for ARVD[11,12]. It would be reasonable to suggest that individuals with an abnormal SAECG should receive close clinical follow-up[18]. Further studies with a long-term follow-up are required to better define the significance of an abnormal SAECG in a normal family member.

Changes in the SAECG parameters during follow-up

The clinical expression of ARVD is postponed until adolescence and young adulthood, and thus the proposed standard criteria for diagnosis cannot be applied until after adolescent growth is completed, as supported by the greater prevalence of abnormal SAECGs as the age increases or during follow-up (Table 3)[6,11]. Serial SAECG recordings appear to be useful in establishing the evolution of the disease in the affected patients[6].

Table 3. Relation between the age, SAECG, and disease[6]

Age (yr)	1→10	11→20	21→30	31→	Total
Number of patients	8	32	13	22	75
Affected patients	2(25%)	18(56.2%)	9 (69.2%)	18(81.8%)	47
No evidence of heart disease	6(75%)	14(43.7%)	4(30.8%)	4(18.2%)	28
Abnormal SAECG in affected patients	1*(12.5%)	13*(40.6%)	8*(61.5%)	17*(77.2%)	39

*p=0.001

Conclusion

The SAECG is one of the essential tests for the evaluation of (suspected) patients with ARVD. However, as other tests, it has some significant limitations. Further research is needed to confirm the value of SAECG testing in predicting the risk of sudden death, assessing the rate of progression, and screening of family members.

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