International Journal of Cardiology 174 (2014) 628–633

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Risk stratification of arrhythmogenic right ventricular cardiomyopathy based on signal averaged electrocardiograms

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ARTICLE INFO

Article history:
Received 27 January 2014
Received in revised form 10 April 2014
Accepted 14 April 2014
Available online 21 April 2014

Keywords:
Signal-averaged electrocardiogram
Arrhythmogenic right ventricular cardiomyopathy
Ventricular arrhythmia

ABSTRACT

Background: Signal averaged electrocardiogram (SAECG) is a specific and non-invasive tool useful for arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis. However, its role in risk stratification of patients with ARVC remains largely undefined.
Methods: Sixty-four patients fulfilling Task Force ARVC criteria (mean age: 47 ± 14 years-old, 56% male, 50% definite ARVC) were enrolled. The baseline demographic, electrocardiographic, structural, and electrophysiological characteristics were collected. Patients with SAECG fulfilling all 3 Task Force criteria (3+ SAECG) were categorized into group 1, and those fulfilled 2 or less criterion were categorized into group 2. The study endpoints were unstable ventricular arrhythmia (VA), device detectable sustained fast VA (cycle lengths <240 ms) and cardiovascular death.
Results: During a mean follow-up of 21 ± 20 months, 15 primary endpoints including 12 unstable VAs and 3 device-detected fast VAs were met. One patient died of electrical storm, and one patient underwent heart transplantation. The presence of 3+ SAECG predicted malignant events in all patients with definite and non-definite ARVC ($p < 0.01$, OR = 30.5, 95% CI = 2.5–373.7) and in patients with definite ARVC alone ($p = 0.03$, OR = 11.1, 95% CI = 1.3–93.9). Patients diagnosed with non-definite ARVC without 3+ SAECG were free from malignant events.
Conclusions: SAECG fulfilling all 3 Task Force criteria was an independent risk predictor of malignant events in ARVC patients. SAECG may play a valuable role in ARVC risk stratification.

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare genetic myocardial disease characterized by progressive fibro-fatty substitution of right ventricular (RV) myocardium and therefore leads to ventricular arrhythmias, congestion heart failure, and sudden cardiac death (SCD) [1–3]. It is one of the major causes of SCD in young people and athletes [4,5]. The clinical diagnosis was defined according to the Task Force criteria, which was being introduced in 1994, and was revised in 2010. This diagnostic criterion is based on a scoring system that comprised 6 main categories, which include depolarization and repolarization of electrocardiogram (ECG) as major and minor components [6–9]. Risk stratification is a key to clinical prognosis and medical management. However, the precise risk stratification has not been fully established by the current diagnostic tools.

Signal averaged electrocardiogram (SAECG) is a non-invasive tool useful for detection of the delayed depolarization from the diseased myocardium [10]. It has been employed to stratify different substrates in ventricular tachycardia (VT) patients [11]. The late potentials can be detectable in approximately 40–60% of ARVC patients in previous clinical trials [12–15]. However, they are rarely manifested in surface ECG. The SAECG can more accurately depict the presence of late potentials when compared to surface ECG; therefore it can provide additional information and guide clinicians in making accurate clinical diagnosis [7,16,17]. It is known that heterogeneous slow-conducted myocardium contributes to the perpetuation of ventricular arrhythmias [14]. In previous studies involving patients with ischemic cardiomyopathy, SAECG-detected late potential has been associated to higher incidence of ventricular tachyarrhythmia and could be used to predict adverse

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http://dx.doi.org/10.1016/j.ijcard.2014.04.169
0167-5273/

clinical events [11,18,19]. We hypothesized that the different severity of SAECG abnormalities could provide additional prognostic information in ARVC patients.

2. Methods

2.1. Study population

Between March 2000 and January 2013, 64 consecutive patients (mean age: 47 ± 14 years, male/female ratio = 36/28) who met at least two minor or one major revised Task Force criteria were enrolled in this non-concurrent prospective study. All the ARVD cases are from the unselected group with consecutive ARVC patient database in our hospital. For all patients, their baseline demographic, structural, electrocardiographic, invasive electrophysiological characteristics and the results of the ablation procedures were collected at the time of enrollment. For the patients enrolled before 2010, their medical records were reviewed retrogradely and their ARVC diagnosis was re-established by the revised Task Force criteria of 2010. Based on the criteria, 32 (50%) patients had definite ARVC, 18 (28%) patients had borderline ARVC, and 14 (22%) patients had possible ARVC.

All patients had resting ECG, SAECG, echocardiography and 24-hour Holter investigations. Magnetic resonance image (MRI), right ventriculography, endomyocardial biopsy, and coronary arteriography were performed in 81%, 81%, 40% and 75% of the patients respectively. The RV function was assessed mainly via cardiac MRI or occasionally by right ventriculography when MRI was contraindicated. Left ventricle (LV) systolic function was assessed via echocardiography. There were three patients with implantable cardioverter defibrillator (ICD) before enrollment.

2.2. Signal averaged electrocardiogram

The revised Task-Force criteria defined positive SAECG if it fulfills one of the three criteria: (1) filtered QRS duration ≥114 ms; (2) duration of the terminal QRS < 40 μV ≥ 38 ms; and (3) root-mean-square voltage of the terminal 40 ms ≤ 20 μV. In the present study, patients were categorized into group 1 ($N = 24$) if the SAECG fulfilled all of the 3 criteria (3 + SAECG), and patients were categorized into group 2 ($N = 40$) if the SAECG fulfilled two or less criteria (0–2 + SAECG) (Fig. 1). The initial SAECG study after enrollment and before radiofrequency ablation procedure was used for analysis. Before obtaining the SAECG, all anti-arrhythmic drugs were discontinued for more than 30 days.

2.3. The revised Task Force criteria

The revised Task Force criteria for the diagnosis of ARVC have been well documented in previous studies [7]. Briefly, the revised Task Force criteria is a scoring system composed by 6 categories including RV structure deformities in MRI, [20] echocardiogram or right ventriculography; depolarization abnormalities in surface ECG or SAECG; repolarization abnormalities in surface ECG, documented clinical arrhythmia arising from RV, pathologically significant fibro-fatty infiltration, and a family history of ARVC. Definite ARVC is fulfilled by the presence of 2 major, or 1 major plus 2 minor, or 4 minor criteria or more from different categories. The presence of 1 major plus 1 minor, or 3 minor criterion leads to the diagnosis of borderline ARVC. Possible ARVC indicated that the patients fulfilled only 1 major or 2 minor criterion. Although some patients were diagnosed before 2010 by the original Task force criteria, we applied the same criteria (Revised Task Force criteria in 2010) to all patients for ARVC diagnosis whenever they are enrolled before or after 2010. For the patients enrolled before 2010, their medical records, image studies and ECG were reviewed retrospectively to re-establish the ARVC diagnosis.

2.4. Electrophysiological study

The majority of the enrolled patients (77%) received at least one radiofrequency ablation procedure for drug refractory symptomatic ventricular arrhythmia. All electrophysiological studies were performed in a non-sedated and fasting state. All anti-arrhythmic drugs except amiodarone were discontinued for minimum 5 half lives before procedure. Sustained VT induction was attempted by programmed RV stimulation (with up to 3 extra-stimuli after 8 paced ventricular cycle lengths). Intravenous isoproterenol (1–4 μg/min) was administered if sustained VT was not inducible by RV stimulation alone. The endpoint of the programmed RV stimulation was induction of sustained monomorphic VT or ventricular fibrillation (VF). Sustained VT was defined as consecutive ventricular activity of more than 30 s or hemodynamically unstable VT less than 30 s requiring immediate cardioversion. The monomorphic VT showed uniform morphology in surface ECG. Polymorphic VT showed beat-to-beat variation. VF was defined as disorganized rhythm without consistently identifiable complexes or a polymorphic ventricular tachyarrhythmia at an average cycle length of <240 ms.

2.5. Mapping and ablation

The mapping procedure utilized to localize the appropriate ablation site included pace mapping during sinus rhythm, endocardial activation mapping, identification of mid-to-late diastolic potentials, and entrainment mapping during VT. In patients with non-

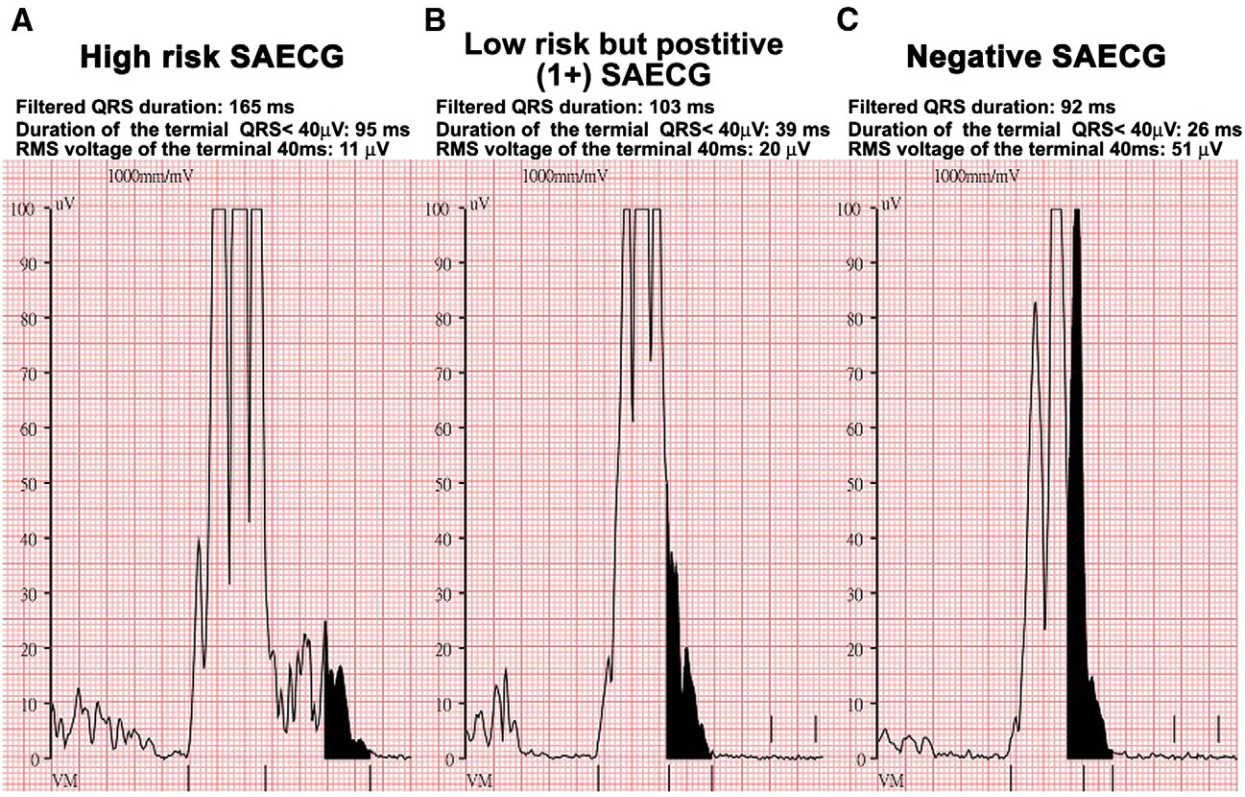

Fig. 1. Example of high risk and low risk SAECG in this study. (A). A sample of a SAECG fulfilling all 3 criteria of the Task Force consensus. A late activation signal is prominent. (B). An example of a positive SAECG fulfilling one criterion. It is a low risk pattern in this study. (C). An example of a negative SAECG fulfilling none of the criterion. It was also a low risk SAECG in this study.