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REVIEW ARTICLE

Epsilon Waves as an Extreme Form of Depolarization Delay: Focusing on the Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

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Abstract: Revision of the Task Force diagnostic criteria (TFC) for arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), in 2010, has increased the sensitivity for the diagnosis of early and familial forms of the disease. Epsilon wave (EW) is a major diagnostic criterion in the context of ARVC/D, however, it remains unquantifiable and therefore, may leave room for substantial subjective interpretation, thus, explaining the existing high inter-observer variability in the assessment of EW. EW, when present, coexists with other disease characteristics, which are sufficient for ARVC/D diagnosis, making EW generally not required for ARVC/D diagnosis. Nevertheless, EW remains an important part of the electrocardiographic phenotype of ARVC/D that may be useful in planning diagnostic work-up, which needs to be recognized.

Keywords: Epsilon wave, arrhythmogenic right ventricular cardiomyopathy/dysplasia, electrocardiography, task force criteria, depolarization delay, ECG.

1. INTRODUCTION

Ever since its first description made by cardiac electrophysiology pioneer Dr. Guy Fontaine in 1977 [1], epsilon wave has been a matter of discussion as to its underlying mechanisms, role in non-invasive characterization of the ventricular arrhythmic substrate, diagnostic value and its importance for risk stratification and clinical decision making.

Even though the electrocardiographic phenomenon is known nowadays as a surface ECG feature observed primarily in the context of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), it was first observed as a distinct depolarization deflection that followed the seemingly completed ventricular activation recorded from the epicardium in a patient with post-infarction ventricular tachycardia (VT) due to a scar located on the inferior left ventricular wall. In a thoroughly performed electrophysiological study, Dr. Fontaine demonstrated continuous activation in the post-infarction scar area, which was not particularly distinct due to the low-amplitude signal. When depolarization wave reached an area of embedded in fibrous tissue, preserved cardiac myocytes sufficient in number for the generation of electrical forces detectable on electrogram, it created the effect of a potential separated from the main ventricular depolarization complex. The phenomenon was initially called "post-excitation potential" and later labeled as epsilon wave [2, 3].

Shortly thereafter, the original report of the first series of patients with ARVC/D was published [4]. Out of those 24 patients, seven had delayed depolarization potentials observed in the right precordial leads on surface ECG, which, by that time, had already received the name "epsilon wave", thus making it an electrocardiographic landmark of ARVC/D.

2. MECHANISMS

The mechanism behind the appearance of the delayed depolarization potential visible on the surface ECG, particularly in patients with ARVC/D, as an epsilon wave is believed to be related to the slow conduction to the islands of working myocardium on the epicardial layers of the ventricular wall embedded in the extensive fibrosis developed in the affected areas of the right ventricle [4, 5]. However, the initial recognition of the epsilon wave, caused by the left ventricular conduction delay, was not visible as a distinct potential that would follow the QRS complex on surface ECG. Since the QRS complex reflects the global ventricular depolarization process, rather than localized phenomena detectable using epicardial mapping, the probability of localized ventricular conduction delay to become visible on surface ECG depends on the localization of the substrate in the ventricles and the sequence of ventricular depolarization. Postinfarction scar and associated conduction delay would, therefore, be hidden within the QRS complex if localized midway in the course of ventricular depolarization and may become visible if it is the latest depolarized area of the ventricular myocardium, such as the subtricuspid area of the right ventricle in patients with ARVC/D [6].

3. DEFINITION

Modern medicine and managed care demand clear cut definitions of disease signs that are free from subjective interpretation in order to be used worldwide for decision mak-

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ing. This is not the case for the epsilon wave, which has undergone an evolution from the time when it was initially described to the contemporary attempts to integrate it in the diagnostic work-up in the context of ARVC/D.

According to the 2010 TFC, epsilon wave is defined as a "reproducible low-amplitude signal between the end of QRS complex to the onset of the T wave in the right precordial leads (V_1 to V_3)" [7]. However, a number of other definitions have existed. According to the original definition of epsilon waves made by Dr. Fontaine, it could be described as "tiny signals ... that consistently occurred after the end of each QRS complex on the surface electrocardiogram" [1] or as "a slur at the end of right precordial QRS complexes" [8]. Epsilon waves have also been described as low-amplitude electrical potentials that occur "at the end of" [9] or "immediately after the QRS complex" in the right precordial leads [9-13], "at the beginning of the ST segment" [14, 15], as "notches buried in the end of the QRS complex" [16], "constant or inconstant small afterdepolarizations in the transition of right precordial QRS complex and ST segment" [17], or "terminal deflection within or at the end of the QRS complexes" [18]. Understandably, a number of publications do not provide any study-specific definition of epsilon wave but rather refer to the Task Force documents [19, 20]. The diversity of definitions suggests that the ECG patterns considered or reported by different research groups as epsilon waves may differ significantly, as also follows from the illustrations available in the literature, which have implications for both the diagnosis of ARVC/D and risk stratification. This was also indirectly supported by a highly variable reported prevalence of epsilon waves in different ARVC/D registries, ranging from <1% to 25% (Table **1**) [21].

Table 1. Prevalence of epsilon wave in different ARVC/D registries [21].

Registry	Total Number of Definite ARVC/D Patients	Patients with Epsilon Waves	Prevalence of Epsilon Waves
North American	108	1	0,9%
Nordic	338	31	9%
Johns Hopkins Hospital	308	28	9%
Italian	147	14	10%
Switzerland	89	22	25%

In order to reconcile the definitions used in different ARVC/D registries worldwide, principal investigators from seven ARVC/D registries in North America and Europe were asked to identify epsilon waves among 30 ECG patterns containing QRS complexes from leads V_1, V_2 and V_3, recorded in patients admitted for a diagnostic evaluation with ARVC/D in question [21]. Only in ten cases, a consensus was reached whether the patterns represented epsilon wave or not. The main reasons for disagreement were differences in interpretation of localization of the "low-amplitude potentials" and whether the end of the QRS complex would be considered in the lead with observed suspected epsilon wave or whether it was the global end of depolarization observed in the presented leads. As an attempt to improve the definition, a second ECG reading was done a few months later and the revised definition was applied. This defined epsilon wave as a low-amplitude deflection occurring after the latest end of QRS complex seen in any of the leads V_1, V_2 or V_3. The number of unanimously assessed ECG patterns increased from 10 to 14, which, however, was still far from perfect.

Several studies have tested the usefulness of alternative approaches for ECG registration and analysis for the identification of epsilon waves. Modified placement of the precordial leads proposed by Fontaine [22] and a recently proposed 16-lead high-definition ECG system [23] appeared to increase the likelihood of observing delayed depolarization potential, otherwise not visible from standard surface ECG. Signal-averaged ECG (SAECG) may also disclose fragmented low-amplitude irregularities in the terminal portion of the QRS complex by amplifying the low-amplitude signal at the end of the QRS complex, which may otherwise be obscured on the standard 12-lead ECG recording [24]. Even alternative ECG recording techniques, such as implantable loop recorders, were proposed for the detection of epsilon waves in patients with ARVC/D [25]. None of these approaches, however, are compatible with the Task Force definition of epsilon waves in its strict sense.

4. ROLE FOR ARVC/D DIAGNOSIS

The importance of the epsilon wave definition is related to the role it plays in the diagnostic work-up and decision making in the context of ARVC/D. Interest in ARVC/D as a cause of sudden death, particularly in the young, has led to a widespread of cascade screening of family members to ARVC/D patients and a growing number of asymptomatic mutation carriers who do not fulfill diagnostic criteria but remain under clinical follow-up. Targeting this patient group was one of the important reasons that lead to the revision of the Task Force criteria in 2010, which increased their sensitivity in order to capture early disease signs and initiate early risk stratification. In this context, the epsilon wave plays a particularly important role since its positive identification may be pivotal for establishing a definite ARVC/D diagnosis using the TFC 2010. For example, an asymptomatic first-degree family member to a patient with ARVC/D can be diagnosed with definite ARVC/D in the absence of visible cardiac structural abnormalities, and otherwise normal ECG if the attending physician interprets fractionation of the terminal part of the QRS-complex as fulfilling epsilon wave definition. While this scenario illustrates a logical imperfection of the diagnostic criteria according to their current definition, it highlights the need for reconsidering the definition of epsilon waves and their role in the diagnosis of ARVC/D.

Given its weight in the ARVC/D diagnostic work-up, it is notable that the epsilon wave remains one of the few 2010 TFC criteria that is not quantifiable, and therefore, may leave room for subjective interpretation. While the classic appearance of epsilon waves in patients with advanced ARVC/D, when a distinct sharp deflection is separated from

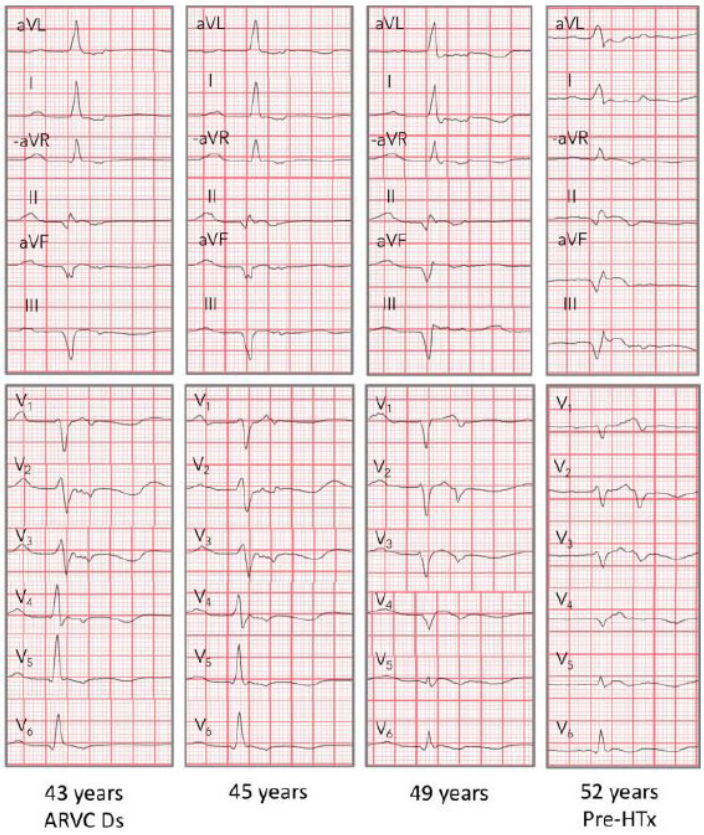

Fig. (1). Progression of ventricular depolarization abnormality in a male patient with ARVC/D over ten years follow-up. It is first seen as a fractionation of the terminal part of the QRS-complex with prolonged TAD in the right precordial leads at age 43, when the patient was first diagnosed. Right ventricular structural abnormalities, which were present at the initial presentation, progressed rapidly to the right ventricular heart failure that ultimately led to heart transplantation (HTx) at the age of 52. The terminal depolarization abnormality observed at the initial presentation eventually developed into a very distinct epsilon wave observed in all chest leads with particularly high amplitude in leads V_1-V_3 and separated from the QRS complex by a low-amplitude signal segment. Note that the time from the onset of the QRS, which remains narrow in its appearance, to the end of the delayed ventricular depolarization signal observed in all 12 ECG leads gradually increases and reached 270 ms at the last ECG taken prior to HTx. ECGs are presented at 50 mm/s paper speed. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

the QRS complex, by an isoelectric line is rarely problematic (Fig. **1**), real-life offers a variety of morphological patterns, in which reaching consensus may be problematic as recently illustrated [21].

The obvious uncertainty in the interpretation of irregularities in the terminal part of the QRS complex raises the question of its value for the diagnosis of ARVC/D. It has been observed that epsilon waves are more likely to be present in patients with marked right ventricular fibrosis and advanced disease [26], who had advanced right ventricular enlargement [27, 28]. In the same multi-register collaborative study, it was observed that in 104 out of 105 patients who reportedly had epsilon waves, other criteria sufficient for establishing definite ARVC/D diagnosis, regardless of the epsilon wave, were present [21]. In nearly 90% of patients with epsilon waves, the 2010 TFC repolarization criteria for ARVC/D diagnosis were fulfilled, which has also been reported earlier [4, 14, 20, 29-31]. The only patient who would not be considered as definite ARVC/D if epsilon wave had to be reconsidered, would still be classified as "borderline ARVC/D" due to the presence of three minor criteria for imaging, family history, and depolarization abnormality. It was also observed that whenever interpretation of the terminal QRS due to suspected epsilon wave came in question, the terminal activation delay (TAD), defined as the time from the S-wave nadir to the end of QRS complex [7], was prolonged over 55 ms and, thus, minor depolarization criterion was fulfilled. The writing group, therefore, suggested that depolarization abnormalities in the right precordial leads should not be interpreted as an epsilon wave if TAD ≥55 ms is not fulfilled.

Defined according to the TFC 2010 criteria, epsilon waves do not seem to contribute to the ARVC/D diagnosis. They represent a rare phenomenon that can only be seen in a minority of patients with ARVC/D, who have advanced stages of the disease when clinical ARVC/D diagnosis is ascertained by other means [2, 21, 26].

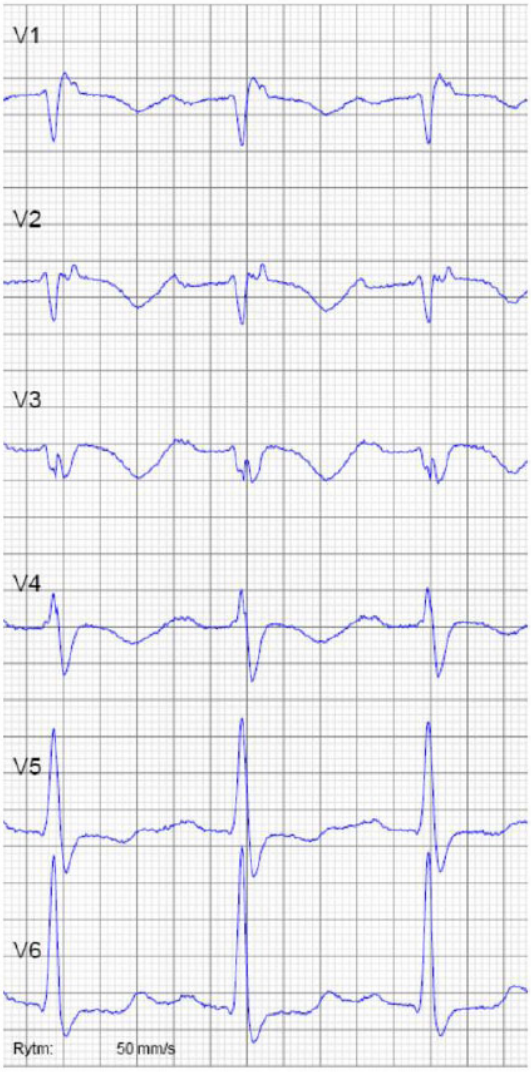

Fig. (2). An example of delayed depolarization potential in the right precordial leads, which met the definition of the epsilon wave that was observed in a patient with pulmonary embolism. Note the clear separation of the distinct spike from the end of the QRS complex in lead V_2. In the lead V_1, the delayed depolarization deflection is merged with the r'. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

5. EPSILON WAVE IN PATIENTS WITHOUT ARVC/D

It is important to acknowledge that epsilon wave has also been described in other situations when the right ventricular myocardium is affected, presumably due to the similar mechanisms related to slow conduction in the free wall and the subtricuspid region of the right ventricle. These include cardiac sarcoidosis [32], myocardial infarction involving the right ventricle [33], tetralogy of Fallot [34], Uhl's anomaly [35], and pulmonary embolism (Fig. **2**).

It is less clear why patients with Brugada syndrome may present with epsilon waves in the right precordial leads either spontaneously [36, 37], during ajmaline challenge [38], or after epicardial ablation of the right ventricular free wall or outflow tract [39], though similar mechanisms of localized conduction slowing in the latest activated right ventricular regions are likely to be involved. The overlapping phenotype of Brugada syndrome and ARVC/D creating diagnostic difficulties have also been reported [40].

6. EPSILON WAVE IN THE CONTINUUM OF THE DEPOLARIZATION DISTURBANCE

Epsilon wave that reflects delayed ventricular depolarization potentials in the right ventricle, visible on surface ECG, represents an extreme form of depolarization abnormality observed in patients with ARVC/D. Localization of the structural substrate in the latest depolarized areas of the right ventricle is the factor that defines the epsilon wave position in relation to the end of ventricular depolarization and its presence

in the right precordial leads, in which abnormalities in the right ventricular free wall and subtricuspid area become visible. Fibrotic transformation of myocardium localized in the earlier depolarized areas of the right or left ventricle would result in the irregularities of the QRS complex observed in its terminal part as terminal slurring of QRS complex, terminal activation delay observed as a prolongation of S-upstroke time [41] or widening of the S-wave angle [42] in the right precordial leads, or fractionation of the midpart of the QRS complex. It appears to be possible to localize the ventricular substrate based on the fractionated QRS presence in the standard 12-lead ECG [43]. Dr. Fontaine's group has proposed an alternative terminology for the description of the fractionated QRS complex in the context of ARVC/D depending on the localization of the additional spikes with QRS complex as "presilon", "topsilon" and "postsion" [2]. While these new electrocardiographic entities define the localization of depolarization abnormalities within the QRS complex, the use of this terminology becomes justified first after ascertainment of ARVC/D diagnosis by other diagnostic modalities since QRS fractionation per se is a highly unspecific sign.

7. EPSILON WAVE IN RISK STRATIFICATION

Given the difficulties in achieving the unambiguous definition of epsilon waves, it is easy to understand the variability of reporting its prognostics value, which is observed in the literature.

While overrepresentation of epsilon waves among high risk patients with ARVC/D has been reported in a few studies [28], it was not a consistent finding across literature [44]. A significant association between epsilon waves and the long-term outcome has been observed [45], however it did not appear to be a useful predictor of arrhythmic risk in any of the primary prevention studies [46-49] and did not qualify for inclusion in the recently proposed risk calculator for patients with ARVC/D [50]. For example, in the most recently published data from the Nordic ARVC registry, epsilon wave was similarly uncommon among patients with secondary (9.5%) *vs.* primary (7.6%) prevention ICD and was not univariately associated with ventricular arrhythmias during follow-up [50].

It is plausible to assume that the greater extent of structural ventricular abnormalities in the right precordial leads associated with pronounced depolarization abnormalities should be associated with the greater arrhythmic risk, however quantification of the ventricular depolarization abnormality remains challenging and objective measures of the ventricular conduction abnormality are still lacking. As of today, epsilon waves do not appear to contribute to risk stratification in ARVC/D.

CONCLUSION

Epsilon wave is an electrocardiographic phenomenon of extreme ventricular depolarization abnormality, which reflects late depolarization of distant myocardial regions caused by the localized fibrotic transformation of myocardial tissue. It is considered to be pathognomonic for ARVC/D but is also observed in other conditions, in which the same myocardial regions are affected. In the context of ARVC/D, epsilon wave is a sign of advanced disease, which does not contribute significantly to the diagnosis of the disease. Low inter-observer agreement, in regard to its definition, further questions its role as a diagnostic criterion for ARVC/D. Though associated with an advanced stage of the disease, none of the contemporary studies have demonstrated prognostic significance of epsilon wave for primary prevention of sudden cardiac death.

LIST OF ABBREVIATIONS

ARVC/D	=	Arrhythmogenic Right Ventricular Cardiomyopathy/dysplasia
ECG	=	Electrocardiography/Electrocardiogram
TAD	=	Terminal Activation Duration
TFC	=	Task Force Criteria
VT	=	Ventricular Tachycardia

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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