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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Should epsilon wave be considered as a major diagnostic criterion in arrhythmogenic right ventricular cardiomyopathy?

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined structural heart disorder characterised by fibro-fatty substitution of the right ventricle (RV). It typically affects RV, but may also involve left ventricle (LV), leading to heart failure or life threatening ventricular arrhythmias [1]. Nevertheless, in some individuals it remains asymptomatic for many years, and the first clinical manifestation is sudden cardiac death (SCD). The diverse presentation and nonspecific nature of the disease make the diagnosis challenging and often ambiguous.

The first report of ARVC was made in the year 1736 by the Pope's physician, Giovani Maria Lancisi, who described a family with pathologic RV in post-mortem examination, heart failure, and SCD in four generations, strongly indicating ARVC [2]. In the year 1977 Marcus et al. [3] observed 'tiny signals (…) that consistently occurred after the end of each QRS complex on the surface electrocardiogram', not yet affiliated with ARVC. It was not until 1982 when the clinical profile of this entity was described, concluding from 24 patients with ventricular arrhythmias of left bundle brunch morphology [3]. Only two years later, the first diagnostic method for ARVC was described. The paper presented electrocardiographic (ECG) characteristics of the disease, namely the diffused intraventricular conduction defects, previously observed by Marcus et al. [3]: the epsilon wave [4].

The epsilon wave represents delayed potentials resulting from slow conduction in the RV, observed most prominently in right precordial leads. The fibro-fatty tissue, present in the RV of ARVC patients, interrupts continuity of the electrical signal. It causes delayed activation of the RV and creates a re-entrant circuit — the anatomical substrate for life — threatening arrhythmias. RV free wall and RV outflow tract are primarily affected and related to arrhythmogenesis of left bundle branch block morphology. Although this is true for the majority of ARVC patients, there is growing clinical evidence that over time LV also adopts the changes observed in RV [5]. This modifies the re-entry circuit and can be observed as variation of the outline of the electrical signal. Hence the more altered is the ventricular conduction the more evident is the epsilon wave. At early stages of the disease it may be undetectable in a standard ECG. Conversely in patients with severe forms of the disease, this finding is typically permanent and can change its form over time. Until then the electrical instability of RV can be followed as late potentials in electrophysiology study or signal-averaged electrocardiography [6–8]. This is an important characteristic because the presence, morphology, and progression of the epsilon wave may provide information on the extent of the disease [9]. Conversely, being the late manifestation of the disease it is unlikely be able to contribute significantly to the disease diagnosis because at the time when epsilon wave becomes apparent on ECG other ARVC manifestations come to the surface and are sufficient for establishing ARVC diagnosis regardless of the epsilon wave [10].

In the 2010 revised Task Force Criteria (TFC) the epsilon wave is defined as a reproductive, low-amplitude deflection, observed on an ECG recording (leads V1–V3) between the end of the QRS complex and the beginning of the T wave [9, 11]. This brief definition gives room for interpretation. Accordingly, depending on the source used, the epsilon wave can be described as: a slur [12] or notches occurring at the end [10, 12, 13] or after [13, 14] the QRS complex or transition of QRS complex and ST segment [15] in the right precordial leads. Additionally, Wang et al. [16] suggested that there are different forms of epsilon waves: wingle waves, small spike waves, and smooth potential waves forming an atypical prolonged R' wave (Fig. 1–3). This makes the epsilon wave one of a few 2010 TFCs that is not quantifiable and apparently highly subjective.

In line with that, Platonov et al. [10] evaluated high intra-observer variability in the interpretation of the epsilon wave. ECG tracings of 30 patients evaluated for ARVC were given to panel members to assess whether they meet the 2010 TFC for ARVC. A unanimous agreement was reached for 33% of the cases only. This low interobserver agreement is hardly acceptable from the clinical point of view, especially given that the epsilon wave constitutes a major ARVC diagnostic criterion. Establishment of the diagnosis of ARVC requires two major criteria, one major and two minor criteria, or four minor criteria. Therefore, any relative of a ARVC patient (major criterion) with depolarisation abnormality interpreted as epsilon wave in ECG recording (major criterion) will meet the diagnostic criteria for definite ARVC.

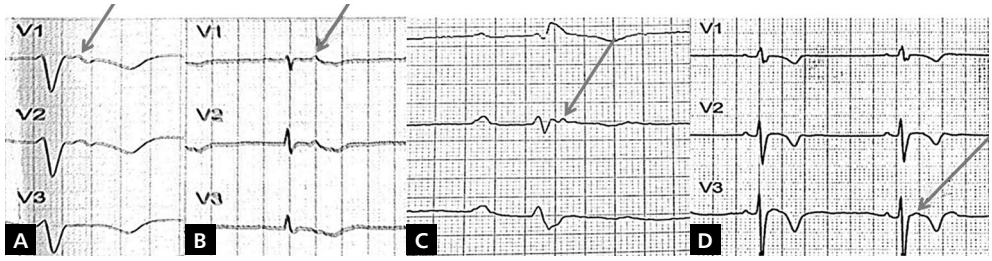

Figure 1. Epsilon "spike" wave: **A.** Typical epsilon "spike" wave seen in V1–V2; **B.** Extreme delay of the epsilon wave (spike type) in a patient with a huge right ventricle; **C.** Spike in V2, winkle in V1, and wide, notched S in V3; **D.** "Spike" epsilon wave seen in V3. Arrows indicate the epsilon wave

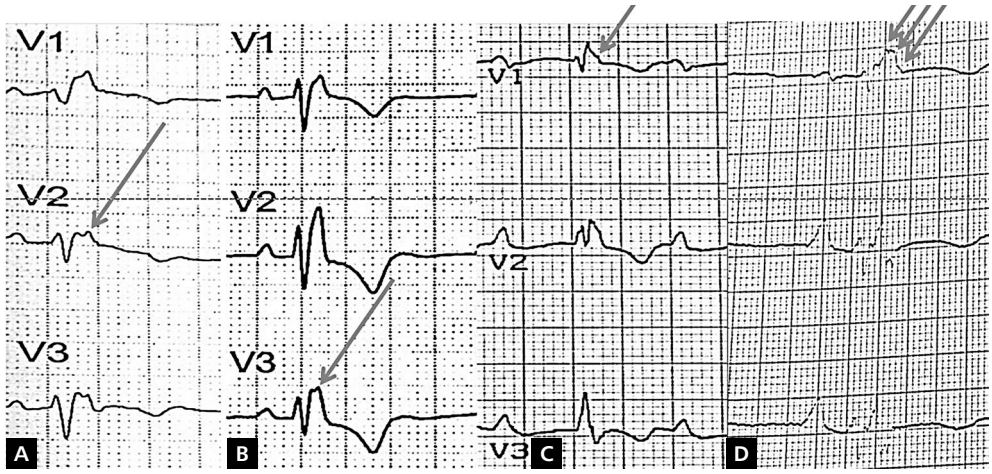

Figure 2. Epsilon "wingle" wave: **A, B, C.** Single wingle wave (**D**) multiple epsilon wave. Arrows indicate the epsilon wave

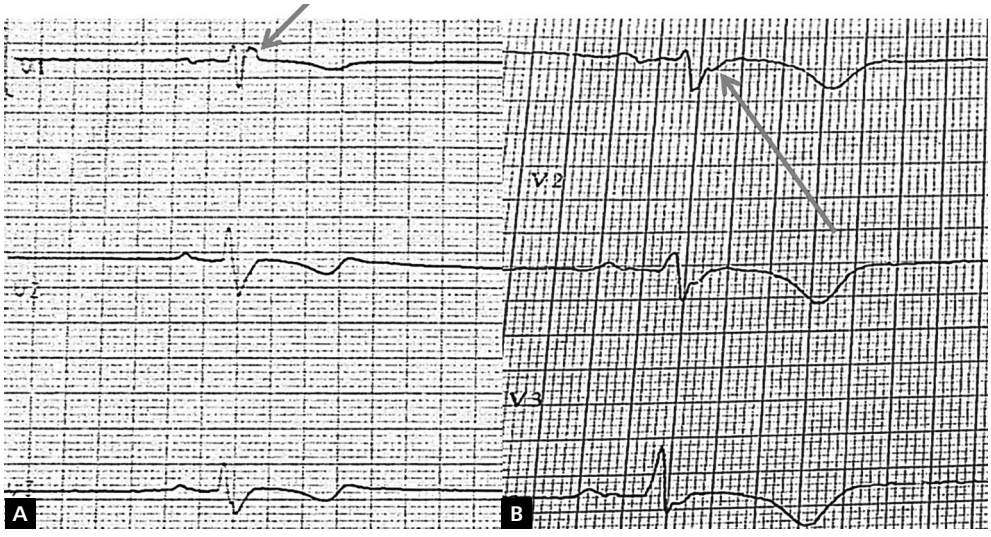

Figure 3. Notched wide S wave: **A.** Wingle epsilon wave in V1 and notched wide S in V2–V3; **B.** Notched wide S in V1–V3. Arrows indicate the epsilon wave

The reported specificity qualified the epsilon wave not only as a major criterion for ARVC diagnosis but also as a hallmark of the disease. It is, however, a relatively rare finding, manifesting itself only in from 1% to 25% of ARVC patients [10]. In large American registries the percentage does not exceed 10%, whereas European registries, examining similar sample groups, report from 10% to 25% detection. This exposes the variability of definitions and interpretations of ECG-patterns suggestive of epsilon wave used across the globe.

In order to increase the epsilon wave detection rate, investigators try to use different methods of receiving ECG recordings. Wang et al. [16] examined a group of 32 consecutive patients diagnosed with ARVC. All patients underwent (1) a standard 12-lead ECG, (2) Fontaine bipolar precordial lead ECG, and (3) right sided precordial lead ECG. The rates of epsilon wave detection by these methods were, respectively: 38%, 50%, and 38% and rose to 66% when all three methods were used. Another method of raising the detection rate, proposed by García-Niebla et al. [17], was increasing cutoff frequency when performing ECG. It is worth noting, however, that the use of alternative leads or non-conventional filter settings aimed at increasing sensitivity for epsilon-wave detection is not covered by the definitions provided in the Task Force 2010 document, and the value of these approaches, and thus epsilon waves detected by them, for ARVC diagnosis should therefore be interpreted with caution. In some cases, however, the abnormalities of ventricular conduction confined to the RV, such as right precordial QRS prolongation [18] or coved-type ST segment elevation in the right precordial leads [19], may lead to difficulties with interpretation of the ECG pattern and increase uncertainty in regard to identification of epsilon wave. Extreme caution should therefore be exercised in cases when ARVC diagnosis is dependent on the interpretation of ventricular depolarisation abnormality pattern. Therefore, it is essential to acknowledge that ECG alone is not sufficient to diagnose or exclude ARVC.

It is important to acknowledge that the epsilon wave is not specific to ARVC only and has been reported in patients with other conditions such as sarcoidosis [20], myocarditis [21], or acute RV infarction [22]. Moreover, an iatrogenic form of epsilon wave has been described, occurring after catheter ablation in the RV [23]. This further supports the concept that the epsilon wave is only a sign of abnormal RV activation and needs to be interpreted in the context of other ARVC manifestations.

In conclusion, the epsilon wave is an ECG phenomenon that reflects delayed propagation of ventricular depolarisation in the RV observed in patients with ARVC and other conditions affecting RV myocardium. Its current definition in the context of ARVC adopted by the 2010 TFC document, however, leaves room for substantial variability in its interpretation. With regard to the epsilon wave weight in the diagnostic work-up as a major diagnostic criterion, the uncertainty of its definition and its late appearance in the course of ARVC, critical re-evaluation of the epsilon wave value as a diagnostic criterion is needed. As the first step in that direction, the isolated epsilon wave was not recommended to be considered as a major criterion in family members undergoing cascade screening when the only other finding is family history for ARVC [10]. Has the time come to take the next step and eliminate the epsilon wave from the diagnostic score?

Its clinical application should not exceed the importance of other indicators of electrical remodelling (e.g. dispersion of QRS duration in the precordial leads, late potentials in SAECG). In addition to that, we are lacking data on the role of late phase of QRS complex elongation and ARVC. Surprisingly, despite the huge progress in ARVC diagnostic techniques [24, 25] over the last few decades, there is still a lot of room for improvement in terms of basic knowledge concerning elementary diagnostic methods — namely ECG.

Conflict of interest: *none declared*

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