Review Article

Epsilon Wave Back in Force

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Abstract

Four decades of progress in understanding the electrogenesis, clinical value and recording methods of the epsilon wave have been achieved since it was first recognized in 1977. According to the new 2010 Task Force criteria, epsilon waves are a major criterion in the diagnosis of arrhythmogenic right ventricular dysplasia. Epsilon waves can be observed in the right precordial leads when a relevant intramyocardial conduction defect is present in the right ventricle. In this paper, we summarize the progress, challenge, and controversies in the definition of epsilon waves.

Keywords: Arrhythmic right ventricular dysplasia, electrocardiogram, epsilon waves, sudden death, Task Force criteria

Introduction

Arrhythmogenic right ventricular dysplasia (ARVD), first described by our group in Paris in 1977,[1] mostly affects the right ventricle (RV) and can be the cause of sudden death in the young and in the athlete.[2-5] Epsilon waves were also described at the same time in patients with ARVD,[1] and less frequently in several other cardiac diseases such as cardiac sarcoidosis, congenital heart disease, or coronary heart disease,[6-11] which lead to a loss of its original value. Therefore, and for other reasons, the 2010 Task Force criteria tried to restrict the epsilon wave to its presence in the right precordial leads V1–V3, which should be a hallmark of ARVD. However, the definition has not been universal and physicians have used different ways to interpret the epsilon wave, which potentially explains the high interobserver variability in assessing epsilon waves.[12]

The epsilon wave can have particular diagnostic value, also in patients with minimal clinical manifestations of the disease or family members undergoing screening for ARVD. However, restricting the epsilon wave to leads V1–V3 as suggested by the 2010 Task Force criteria leads to a rather low incremental diagnostic value, although increasing its diagnostic specificity.[13] A broader definition of epsilon waves can increase diagnostic sensitivity but needs to be based on the electrophysiologic and pathophysiologic substrate leading to epsilon wave electrogenesis. This pathologic substrate is the result of trouble in development, which was reproduced in the laboratory *in vitro* by an induced pluripotent stem cell model with cardiomyocytes harboring a desmosomal mutation.[14] A variable amount of thin strands of interstitial fibrosis starting in the human embryo is also a feature of this disease [Figure 1].[15] This phenomenon predominantly located on the RV shows an extension to the left ventricle in the vast majority of cases.[2,5,16] This explains that the electrocardiogram (ECG) of ascertained ARVD patients shows an increased QRS duration in all ECG leads, particularly in the right precordials and epsilon waves [Figure 2].[4,17-19]

Progress, Challenge, and Controversies

The right precordial leads are more sensitive to detect epsilon waves in ARVD since ARVD is involving predominantly the RV [Figure 3].[2,16] The typical ECG in Figure 3 was obtained from a young man with ARVD. The ECG tracings of this patient showed obvious epsilon waves in the right precordial leads as opposed to the left precordial leads. This particular arrhythmogenic substrate of ARVD was able to explain the electrogenesis of a sharp high amplitude of unexpected delayed potentials recorded on the epicardium of a patient as previously reported.[20] A reproducible highly fragmented

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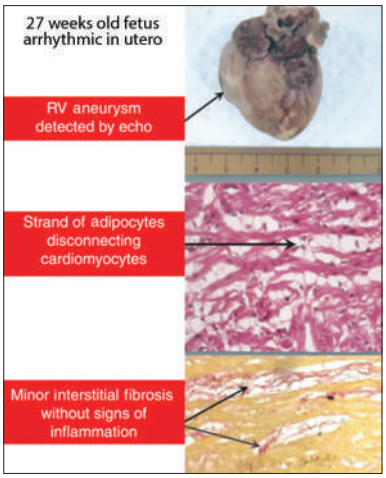

Figure 1: Embryology of arrhythmogenic right ventricular dysplasia. Evidence of a right lateral aneurysm of a 27-week-old fetal heart, arrhythmogenic *in utero*. Histology shows evidence of adipocytes interspersed with myocardial fibers. Minor fibrosis but no signs of inflammation were observed. Hematoxylin phloxine saffron stain, ×400. RV=Right ventricle. With permission from Dr. Guy Hugues Fontaine

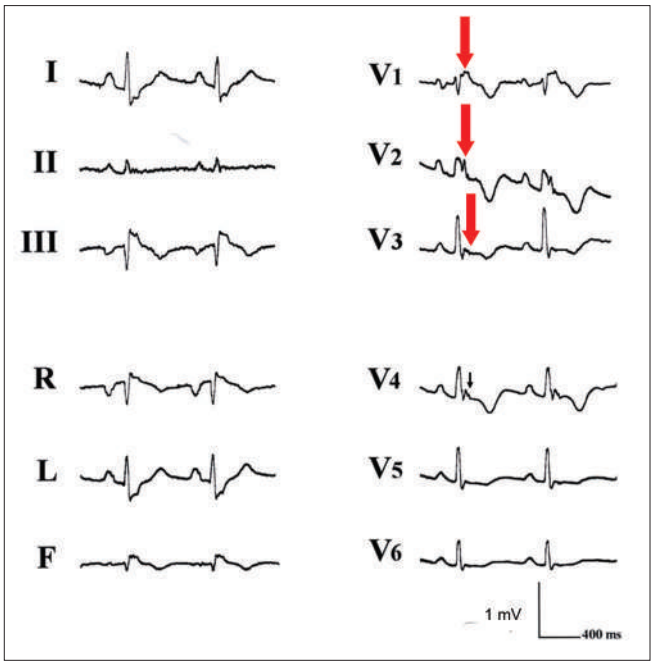

Figure 2: The ECG tracings were obtained from a patient with histologically proved ARVD. Increased QRS duration including epsilon waves is visible. Arrow: Epsilon waves. ECG=Electrocardiogram, ARVD=Arrhythmogenic right ventricular dysplasia. Provided by Dr. Guy Hugues Fontaine

epicardial potential was also recorded on the same patient by a double hook reference electrode occurring 150 ms after the beginning (and clearly after its end) of the surface ECG QRS complex. More impressively, there was delayed activity occurring up to 300 ms after the beginning of the surface QRS complex recorded by a tripolar (1.2 mm apart) exploring electrode system. This surprising electrical signal occurring late after the end of the ventricular refractory period was present after each sinus beat but was not able to reactivate adjacent myocardium despite its high amplitude. Therefore, this electrical activity in a zone of normal myocardium (sharp and high amplitude electric signal) was surrounded by inert nonconductive tissue such as fibrosis or fat. In the same patient, mapping during induced ventricular tachycardia was able to show the same phenomenon of delayed activity at different intervals in between QRS complexes during ventricular tachycardia over the infundibulum of the extremely thin RV typical of Uhl's anomaly.

The experience in the treatment of resistant ventricular tachycardia led to the demonstration of a re-entrant phenomenon. However, because of the presence of the previous nonconducted potential, it was impossible to be certain that the critical pathway used by the re-entrant loop was perfectly identified. This ascertainment came years later after the discovery of the concept of concealed entrainment.[21] However, it was documented for the first time that this major delayed activity can be the background of a re-entrant phenomenon, which can be extended to all forms of ventricular tachycardia, which were induced and interrupted by electrical stimulation. The phenomenon of "postexcitation" was also observed in patients with resistant ventricular tachycardia in idiopathic dilated cardiomyopathy and ARVD. This delayed potential was called the "epsilon waves," the marker of a postexcitation phenomenon.[1,22]

The name "epsilon wave" was given because (1) it is small in amplitude, (2) it is a "postexcitation" phenomenon that mirrors the "pre-excitation" delta wave of the Wolff-Parkinson-White syndrome at the beginning of each QRS complex, (3) and it is the next Greek letter after "delta."[1,22,23]

Analyzing ECG and Holter tracings of the patient with Uhl's anomaly[20] also showed a very small abnormal signal on the ST segment with the same coupling interval as the impressive delayed epicardial potential. Therefore, the same term of "epsilon wave" could also be extended to the signal recorded on the surface ECG and Holter ECG. Because this phenomenon was present on the epicardium and suspected on the bipolar chest lead for Holter recording, it was speculated that this signal not visible on standard ECG leads can be extracted by signal processing leading to the first signal-averaged ECG document.[1,23] Finally, all these tiny potentials recorded on the epicardium with a bipolar chest lead and with signal-averaged ECG could also be named "epsilon waves." It was later understood that this phenomenon was observed on the right precordial leads recording abnormal activation of the RV in patients with ARVD. In these patients, the genetically determined presence (and not necessarily replacement) of fibro-fatty tissue was mostly located on the epicardium as opposed to the endocardium.[2,4]

The technique to exhibit the small amplitude epsilon potential can be improved with a standard ECG machine by increasing the amplitude to the maximum permitted. An example with an amplification of 3 cm/mV was to extract this delayed

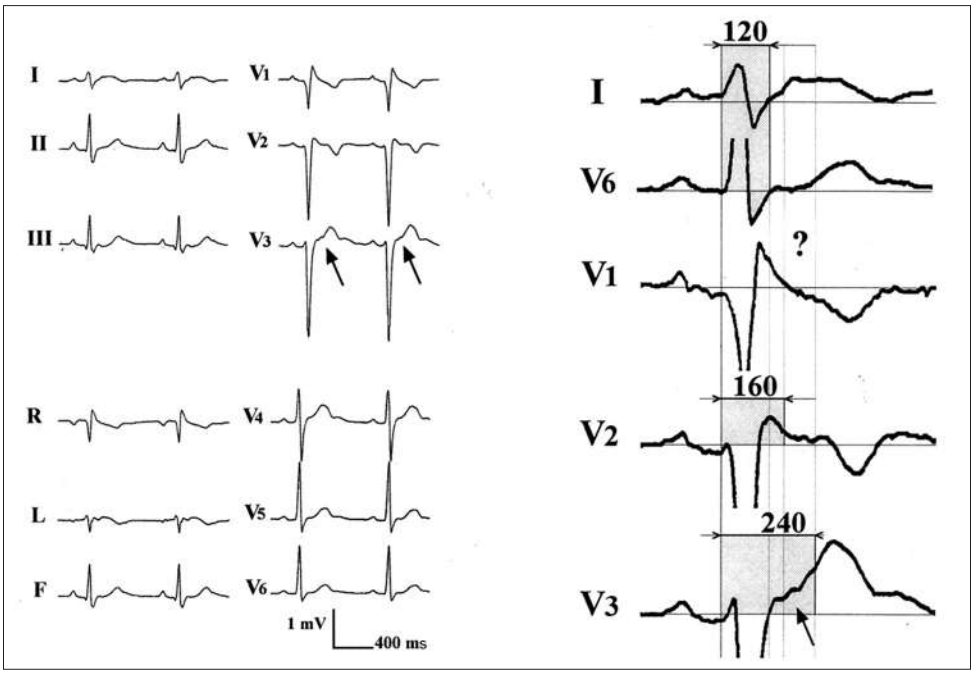

Figure 3: Typical ECG from a young man with ARVD with enlargement of some leads to stress the epsilon wave in right precordial leads as opposed to the left precordial leads. A so-called "more than complete right bundle branch block," meaning that an epsilon wave present on top of RBBB is apparent in the right precordial leads. The "?" sign stresses the limits of epsilon wave detection on a single lead. Arrows: Epsilon waves. ECG=Electrocardiogram, ARVD=Arrhythmogenic right ventricular dysplasia, RBBB=Right bundle branch block. With permission from Dr. Guy Hugues Fontaine

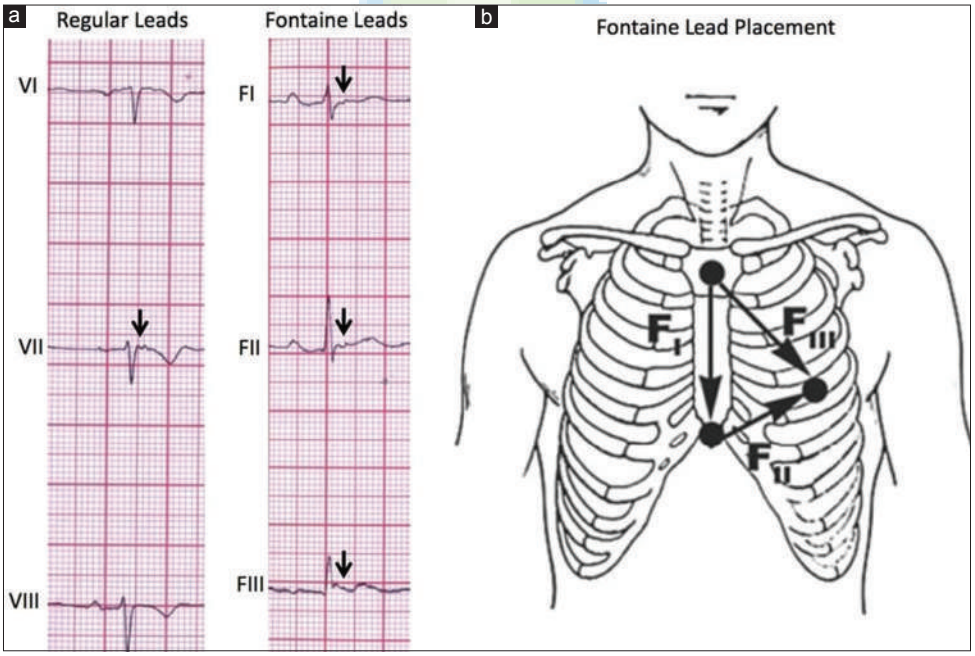

Figure 4: (a) Comparison of regular lead placement *versus* Fontaine lead placement to detect epsilon waves (black arrows). Using the Fontaine lead placement increases the sensitivity of detecting epsilon waves so that they are detected in three leads (FI, FII, FIII) rather than one lead in the regular placement. (b) Fontaine bipolar precordial lead placement. In this modified technique, the ECG should be recorded at double speed (50 mm/s) and double voltage (20 mm/s) to improve the sensitivity for detection of epsilon waves. ECG=Electrocardiogram. With permission from Dr. Guy Hugues Fontaine

activity.[24] Another example shows the effect of an increase of amplification associated with double speed and double voltage of the recording machine [Figure 4].[25-27] In addition, the differences between a thermosensitive paper and an inkjet recorder show a more detailed recording.[25] Finally, the proper arrangement of three bipolar electrodes at the two extremities of the sternum plus a lead on the left precordium was the background of the so-called "Fontaine Lead System."[4,22,28]

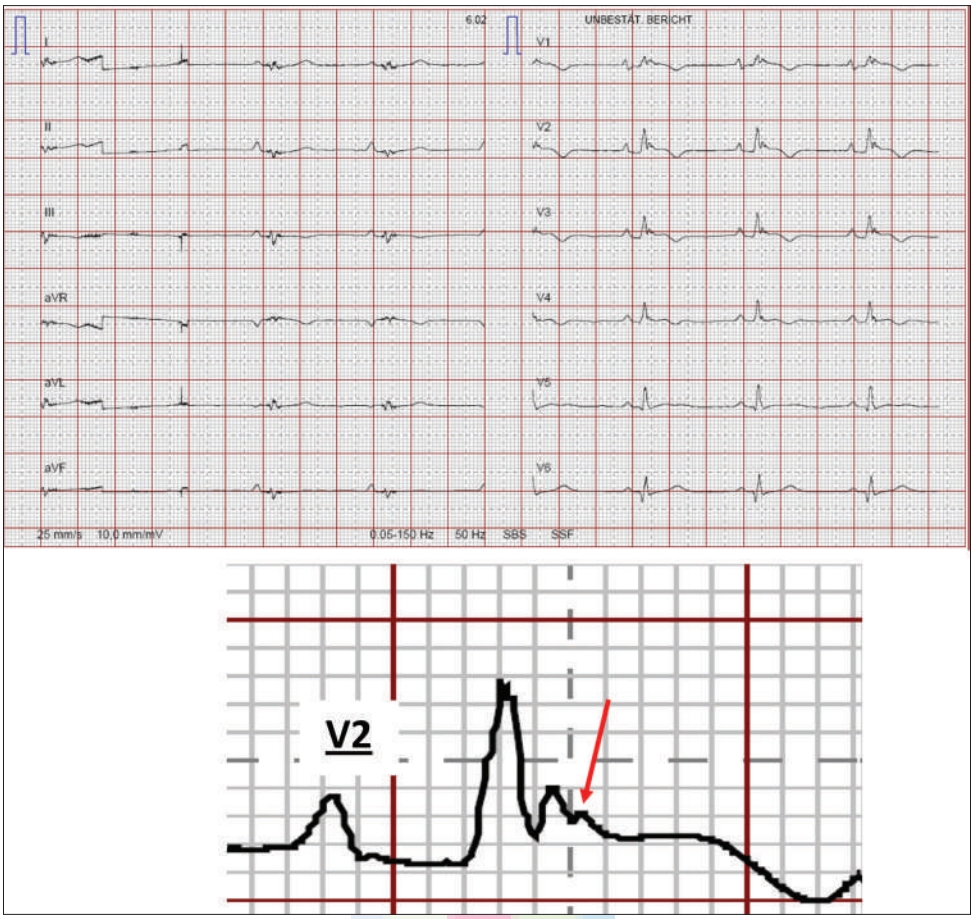

Figure 5: ECG from patients with ARVD shows an obvious more than complete RBBB and characteristic QRS fragmentation including epsilon waves. The magnification extracted from the above ECG indicates epsilon wave (red arrow). ECG = Electrocardiogram, ARVD = Arrhythmogenic right ventricular dysplasia, RBBB = Right bundle branch block. Provided by Ardan M. Saguner

The behaviors of epsilon waves on the epicardium during ventricular tachycardia and during ventricular stimulation have confirmed the concept of intraventricular reentry phenomenon showing a larger coupling at increasing rate leading to the induction of ventricular tachycardia, the role of amplitude of delayed potential suggesting a concealed from a nonpropagated extrasystole leading to a propagated extrasystole visible on the surface tracing was related to an epsilon wave of higher amplitude.

Our group later published two papers[20,29] to stress the results on two series of patients were notable. The papers published intentionally in the French literature aimed to give credit to the country of origin of epsilon waves. In our first reported series of 15 ARVD patients, epsilon waves were associated with a right bundle branch block (RBBB), which may particularly increase the QRS complex duration in the right precordial leads as opposed to the left precordials. This particular aspect was called "more than complete RBBB" [Figure 5].[19] This phenomenon can be also observed in a patient with incomplete RBBB. This study was extended on a larger series of 43 patients.[29] In this study, measurement of a QRS interval longer than 110 ms in sinus rhythm in lead V1 in an individual with an apparently normal heart enabled identification of the disease with a sensitivity of 55% and specificity of 100% if used alone, and a sensitivity of 60% if used in combination with a prolongation of QRS in lead V3 to >110 ms, but with a specificity of 82%. However, if cases with RBBB were eliminated, the sensitivity dropped to 50%. It is noted that this study was performed in a tertiary care center suggesting that the same results can be different in the population at large.

In Naxos disease,[30-32] which is the recessive form of ARVD in which both parents have the same desmosomal plakoglobin mutation,[33] the homozygous nature of this disease shows a more severe alteration of ECG with giant or mega epsilon waves again more visible in the right precordial leads. Epsilon waves are the result of delayed conduction in myocardium independent of the His-Purkinje conduction system. However, the troubles in conduction can be observed in the same patient. This association led to the new terminology of "more than complete RBBB."[29] Another study[32] indicated the same phenomenon. This work mostly based on the epsilon wave stressed the value of this new ECG sign which can be observed in any situation in which there is a delayed activation of myocardium by multiple causes from sarcoidosis to coronary artery disease, but which remains a strong marker of ARVD in a young patient who has a normal heart by standard physical

examination, especially if this depolarization abnormality is also associated with repolarizations anomalies visible in the right precordial leads. It is important to keep in mind that the possible sequel of superimposed myocarditis on top of ARVD can be seen in any ECG lead and any part of the QRS complex.[34,35] These alterations consist of notches or QRS fragmentation, which can be associated with or even superimposed on the typical ECG pattern of ARVD consisting of epsilon waves or T wave inversions.

Conclusion and Perspective

Experiences for the increased sensitivity of detection of epsilon waves using the "Fontaine Lead System" have been reported.[23,26,28,36] Our team reported the first identification of epsilon waves recorded on an implantable loop recorder.[17] Recently, we also first identified the potential of the new Schiller 16 Lead High Definition ECG machine (Schiller, CS-200 Excellence, Baar, Switzerland) to record epsilon waves.[36] The possible sequel of superimposed myocarditis can be seen in any lead, and any part of the QRS complexes and these alterations consist of notches and delayed potentials, which can be associated or even superimposed on the ECG pattern of ARVD. This phenomenon of genetically determined susceptibility of dysplastic myocardium to inflammation has been recently demonstrated to occur by the same desmosomal gene, which has produced the "trouble in development."[34]

The term epsilon wave is frequently used by people who may not be aware of the most recent definition of this term as suggested by the 2010 Task Force criteria, and the broader definition of Prof. Guy Hugues Fontaine (slurred upstroke in any lead or small amplitude potential after the end of the QRS prior to the onset of the T wave in any surface ECG lead). Recently, published data may help people better understand the potential of epsilon waves in ARVD.[23,36-38] Therefore, after the progress in the understanding and proper denomination of ARVD and epsilon waves over the past four decades, it can be said that epsilon waves are back in force as a useful marker to identify ARVD.

Acknowledgments

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Conflicts of interest

There are no conflicts of interest.

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