High Interobserver Variability in the Assessment of Epsilon Waves: Implications for Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia.

Platonov, Pyotr; Calkins, Hugh; Hauer, Richard N; Corrado, Domenico; Svendsen, Jesper H; Wichter, Thomas; Katarzyna Biernacka, Elżbieta; Saguner, Ardan M; Te Riele, Anneline; Zareba, Wojciech

Published in:
Heart Rhythm

DOI:
10.1016/j.hrthm.2015.08.031

2016

High Interobserver Variability in the Assessment of Epsilon Waves: Implications for Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Platonov: Epsilon wave in ARVC/D diagnosis

Pyotr G. Platonov MD, PhD[1]; Hugh Calkins, MD[2], Richard N. Hauer, MD, PhD[3]; Domenico Corrado, MD, PhD[4]; Jesper H. Svendsen, MD, DMSci[5]; Thomas Wichter, MD[6]; Elżbieta Katarzyna Biernacka, MD, PhD[7]; Ardan M. Saguner, MD[8], Anneline te Riele, MD[9]; Wojciech Zareba, MD[10]

No conflict of interests.

1 - Department of Cardiology, Clinical Sciences, Lund University and Arrhythmia Clinic, Skåne University Hospital, Lund, Sweden; 2 - Department of Cardiology, Johns Hopkins Hospital, Baltimore, MA, USA; 3 - ICIN-Netherlands Heart Institute, Utrecht, The Netherlands; 4 - Department of Cardiac, Thoracic and Vascular Sciences, University of Padua Medical School, Padua, Italy; 5 - Danish National Research Foundation Centre for Cardiac Arrhythmia (DARC), Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, and Department of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark; 6 - Department of Cardiology, Heart Center Osnabrück - Bad Rothenfelde, Niels-Stensen-Kliniken, Marienhospital Osnabrück, Osnabrück, Germany; 7 - Department of Congenital Heart Diseases, Institute of Cardiology, Warsaw, Poland; 8 - Department of Cardiology, University Heart Center, Zurich, Switzerland; 9 -Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands; 10 - University of Rochester Medical Center, Rochester, NY, USA

Corresponding author address:
Prof. Pyotr G Platonov, MD, PhD, FHRS
Department of Cardiology, Lund University
22185 Lund, Sweden
Tel: +46 46 172435
Fax: +46 46 157857
E-mail: Pyotr.Platonov@med.lu.se

Total word count: 4697

Subject Codes:

16 [Myocardial cardiomyopathy disease];

171 [Electrocardiology]

Abstract:

Background: Revision of the Task Force diagnostic criteria (TFC) for arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) has increased their sensitivity for diagnosis of early and familial forms of the disease. Epsilon wave (EW) is a major diagnostic criterion in the context of ARVC/D, which, however, remains not quantifiable and therefore may leave room for substantial subjective interpretation.

Objective: To assess interobserver agreement in regard to the EW definition, and EW importance for ARVC/D diagnosis.

Methods: ECG tracings depicting leads V1, V2 and V3 collected from subjects evaluated for ARVC/D (n=30) were given to panel members, who were asked to respond whether ECG patterns meet EW definition outlined by TFC. The prevalence and importance of EW for ARVC/D diagnosis was assessed in a pooled dataset of patients with definite ARVC/D from European and American ARVC/D registries (n=815).

Results: Number of ECG patterns identified as EW varied from 5 to 18 per reviewer (median 13). Unanimous agreement was reached for only 10 cases (33%), 2 of which qualified as EW and 8 as not EW by all panel members. From a pooled dataset, 106 patients reportedly had EW (13%). In 105 of 106 patients with EW (99%) exclusion of EW from the diagnostic score would not affect the "definite" diagnostic category.

Conclusion: Interobserver variability in assessment of EW is high, however the impact of EW on ARVC/D diagnosis is negligibly low. The results urge to extreme caution in assessment of EW presence, especially in patients who would not fulfil diagnostic criteria otherwise.

Key words: epsilon wave, arrhythmogenic right ventricular cardiomyopathy/dysplasia, electrocardiography, interobserver variability, task force criteria

List of abbreviations

ARVC/D	arrhythmogenic right ventricular cardiomyopathy/dysplasia
ECG	electrocardiography/electrocardiogram
EW	epsilon wave
ISHNE	International Society for Holter and Noninvasive Electrocardiology
TAD	terminal activation duration
TFC	Task Force criteria

Introduction

Introduction of the revised diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) in 2010[1] has reflected the molecular genetic and clinical progress made after the original criteria were introduced in 1994[2]. In addition, to minimize subjectivity in imaging and tissue characterization, quantification of right ventricular imaging findings and morphometric analysis of histology preparations has improved the strictness of some of the major and minor diagnostic criteria that compose the 2010 revised Task Force Criteria (TFC). These improvements increase sensitivity in identification of early and familial forms of the disease.

Characteristic abnormalities of ventricular depolarization and repolarization are important components of the diagnostic criteria for ARVC/D. Establishment of the diagnosis of ARVC/D requires 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria. Because of this, for example, patients undergoing downstream testing for ARVC/D following diagnosis of ARVC/D in a first-degree relative to a patient with ARVC/D (a major criterion by Family history), will meet diagnostic criteria for ARVC/D if one additional major criterion is observed on subsequent diagnostic test. One of these major criteria is the presence of an epsilon wave. It is therefore important to be sure that epsilon waves, as assessed on a 12 lead ECG, can be diagnosed accurately. However, 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.

According to 2010 TFC, epsilon wave is defined as a "reproducible low-amplitude signal between end of QRS complex to onset of the T wave in the right precordial leads (V1 to V3)"[1]. This definition evolved from the originally described in 1977 by Guy Fontaine's observation of "tiny signals ... that consistently occurred after the end of each QRS complex on the surface electrocardiogram"[3] or as "a slur at the end of right precordial QRS complexes"[4]. Epsilon waves have also been described as low-amplitude electrical potentials that occur "at the end"[5] of or "immediately after the QRS complex" in the right precordial leads[5-9], "at the beginning of the ST

segment" [10, 11], as "notches buried in the end of the QRS complex"[12], "constant or inconstant small afterdepolarizations in the transition of right precordial QRS complex and ST segment"[13], or "terminal deflection within or at the end of the QRS complexes"[14]. Understandably, a number of publications do not provide any study-specific definition of epsilon wave but rather referring to the Task Force documents[15, 16]. Nevertheless, available publications suggest that there is a variation in epsilon-wave definition in regards to the appearance and exact location of the epsilon-potentials.

Increasing appreciation of the importance of ARVC/D as an important sudden death risk factor has led to explosive growth of ARVC/D-related research worldwide and highlighted the necessity of assessment whether epsilon waves are defined uniformly across different cohorts. The aim of the present Epsilon Wave Initiative by the International Society for Holter and Noninvasive Electrophysiology (ISHNE) undertaken by the writing group was (1) to assess interobserver agreement of the epsilon-wave identification and (2) assess the importance of epsilon wave for ARVC/D diagnosis in the national and international ARVC registries represented by the writing group members.

Methods

Construction of dataset for ECG readings

Thirty ECG tracings were collected from ARVC/D patients and family members screened for ARVC/D in the Nordic ARVC Registry[17] (n=21) and high-resolution ECG examples available from the literature[8, 14, 15, 18] (n=9). Seven panel members (HC, WZ, DC, TW, RH, JS, KB) were asked to express their opinion in regard to each of the ECG examples and answer "Yes" or "No" the question whether the tracing would be considered as an epsilon wave based on the 2010 TFC definition. Only QRST-complexes from leads V_1, V_2, and V_3, on which the current definition of epsilon wave is based, were provided to the panelists. Case report form contained additional statements aimed to assess interobserver agreement in the interpretation of the 2010 TFC

definition, for which panelists were asked to respond (1) whether low-amplitude signal is present after the end of QRS or within QRS borders and (2) whether the low-amplitude signal was present in leads V1, V2 and V3 or only in some, but not all leads (V1-V3).

Evaluation of interobserver agreement in assessment of ECG patterns

Upon receipt of the ECG readings, the results were processed by a panel member not involved in ECG reading process (PGP) in order to identify ECG patterns for which there was a consensus (i.e. all panelists making the same classification) or agreement (i.e. ≥6 ECG readers making the same classification) in regard to the ECG pattern assessment as either epsilon wave or not. Those ECG patterns, for which there was a diversity of opinions (i.e. ≤5 ECG readers agreeing on pattern classification), were assessed for possible causes of discrepancies based on the responses that concerned individual characteristics on the low-amplitude signal localization in relation to the end of the QRS complex and ECG leads. Results were reviewed during a face-to-face meeting of the panel members, during which ECG patterns were reviewed and attempt was made to reconcile difference in assessment of the ECG patterns.

After the reconciliation discussion, ECG reading was repeated on a modified ECG data set based on the same ECG examples rearranged in a random sequence. The second ECG reading was performed six months following the first one. The same definitions were used for assessment of agreement in regard to interpretation of the ECG patterns.

Assessment of diagnostic value of epsilon-waves across ARVC registries

The second ECG reading round was followed by an analysis of the importance of the epsilon wave in diagnosing ARVC/D by identifying the patients within these registries that met diagnostic criteria for definite ARVC/D. It was then determined for each of these patients that if the epsilon wave was deleted from TFC, whether this would result in the patient being reassigned to other diagnostic categories (i.e. borderline, possible or no ARVC/D).

Panel participants representing large ARVC/D registries who volunteered to participate in this

cross-sectional analysis (Johns Hopkins Registry - HC; North-American Registry - WZ; Swiss Registry- SA; Italian Registry – DC and Nordic Registry - JHS) were asked to share diagnostic information on subsets of patients with Definite ARVC/D diagnosis and major depolarization criterion fulfilled, i.e. who had epsilon waves on surface ECG diagnosed in accordance with local practices. Substudy participants were also asked to provide a total number of ARVC/D patients with definite ARVC/D diagnosis in order to estimate the prevalence of epsilon wave among ARVC/D patients across different registries.

Ethical considerations

ECG tracings used in this study were collected as a part of the Nordic ARVC/D Registry research protocol approved by the Regional Ethics Review board at Lund University, Sweden (approval #2010/568). Secondary analyses performed on the data from national ARVC/D registries have been compliant with the relevant national regulations and institutional review board approvals. The study complies with the Declaration of Helsinki.

Results

Interobserver agreement in regard to the epsilon-wave assessment: 1st ECG reading

Consensus (all panel members in agreement)

Of the 30 ECG examples, complete consensus between panel members was reached for 10 cases, 2 of which were unanimously identified as epsilon waves and 8 as not epsilon waves. Number of ECG patterns identified as epsilon waves by individual reviewers varied from 5 to 18 (median 13). Results of the ECG assessment are graphically illustrated in Figure 1.

Agreement (at least 6 panel members in agreement)

By applying less strict criteria for assessment of interobserver agreement (≥6 panel members being in agreement upon ECG pattern classification), general agreement was reached in regard

to 25 ECG patterns, 8 of which were identified as epsilon waves (Figure 2) and 17 as not (Figure 3).

The most common reason for disagreement was interpretation of the low amplitude deflection location in regard to the end of the QRS complex. In regard to the 8 ECG patterns generally agreed to represent epsilon waves, panelists who were not in agreement with the majority (n=4) did not consider the low amplitude deflection located after the end of QRS complex and commented that it was either not ”distinct” or not ”separated” from QRS complex. Notably, 7 of 8 ECG patterns recognized as epsilon waves had distinctly negative T-waves in all three leads V1-V3. The identities of panelists who had divergent opinion differed from case to case.

Disagreement

In 5 cases no agreement could be reached. For each of these cases (Figure 4) four panelists identified them as epsilon waves while three did not. The panelists who voted for and against recognizing ECG patterns as epsilon waves differed from case to case. Review of the case-specific assessments and comments aimed at identification of possible reasons for discrepancies showed that the single most important reason for it was difference in assessment of the low amplitude deflection location in relation to the end of QRS complex (Figure 5). In all 5 arguable cases those panelists who did not consider the pattern as epsilon wave, it was assessed as not located after QRS complex or ”not clearly separated from QRS complex”.

Modification of epsilon wave definition and its impact on ECG assessment: 2nd ECG reading

As a result of the outcome of our initial analysis reported above, the writing group members met to refine the definition for epsilon waves in hopes that the new revised epsilon wave definition may result in greater reproducibility in the assessment of epsilon waves. This revised definition explicitly defined epsilon wave as a low-amplitude deflection occurring after the end of QRS defined as the latest end of QRS complex seen in any of the leads V_1, V_2 or V_3. Panelists were then asked to reassess the same set of ECG patterns in a randomly rearranged sequence using the

clarified definition of the QRS end as above. Five additional ECG cases were added into the dataset in random (but not considered for comparison of assessment results between the first and the second readings). In order to assess whether the assessment of epsilon-wave as an entity distinctly separated from the end of the QRS complex can be done similarly by different observers, the panelists were asked to comment whether they judge epsilon wave, if present, being separated from the QRS by an isoelectric interval.

The results of the second ECG reading revealed that consensus was reached for 14 cases, 4 of which were identified as epsilon waves and 10 as non-epsilon patterns. No agreement was reached for 5 of 30 ECG patterns. The number of ECG patterns identified as epsilon waves by individual reviewers, however, still varied greatly from 5 to 16 (median 11 per reviewer).

Of the 8 ECG patterns identified as epsilon waves in the 1st ECG reading, 5 were still identified as epsilon waves as by six or more panelists, while 3 became uncertain. Of 17 ECG cases identified as non-epsilon patterns in the 1st reading, only one became uncertain while 16 were still recognized as non-epsilon patterns. Panelists observed isoelectric interval between the end of QRS complex and epsilon wave in 36-100% of positively identified epsilon-waves (median per reviewer 71%).

Epsilon wave prevalence and contribution to ARVC diagnosis in registries worldwide

The total number of patients with definite ARVC/D by 2010 TFC reported by Johns Hopkins, Nordic, Swiss, Italian and North-American ARVC/D Registries was 815. Out of the total number of ARVC patients, 105 had an epsilon wave, which is the only major depolarization criterion. The overall prevalence of this ECG marker was 13% (ranging from a 1% to 25% among the registries examined, see Table 1 for details).

Exclusion of the depolarization criterion (both major and minor) from the diagnostic criteria for ARVC/D would result in 10 of the 105 patients loosing their definite ARVC diagnosis classification. However all of them would still fulfill minor depolarization criterion (Terminal

Activation Duration (TAD)≥55 ms) and therefore 9 of the 10 would still have sufficient score to be diagnosed as definite ARVC/D patients. The only patient who would not be considered as definite ARVC/D if epsilon wave had to be reconsidered, one would still be classed as having borderline ARVC/D because of the presence of three minor criteria for imaging, family history and depolarization abnormality. In total, in 104 of 105 patients with definite ARVC/D (99%), the diagnostic category (i.e. "definite ARVC/D") does not depend on the presence of the epsilon wave or the way it is judged by individual investigator (Figure 6).

Of the 104 patients who met ARVC/D diagnostic criteria independent on the presence of epsilon-wave, the vast majority fulfilled imaging (87% major and 6 % minor), repolarization (73% major and 16% minor) or arrhythma (44% major and 43% minor) criteria.

Discussion

Main findings

To the best of our knowledge, this is the first study to report interobserver variability of the epsilon-wave definition interpretation performed by principal investigators of large ARVC/D registries in Europe and North America. Our main finding is the surprisingly low agreement in regard to interpretation of epsilon waves based on review of ECG patterns depicting QRS-abnormalities in leads V_1, V_2 and V_3, which had not improved after case by case ECG review and an attempt to refine the definition of the QRS end, which appeared to be a key issue in assessment of epsilon wave presence. However, the importance of epsilon wave for diagnosis appears to be low as 99% of patients with positively identified epsilon waves in the large ARVC/D registries represented in our study do fulfill diagnostic criteria for definite ARVC/D even without epsilon wave and therefore do not need it for diagnosis. This observation indicates that the epsilon wave is usually a manifestation of advanced disease.

Clinical implications of uncertainties in epsilon wave definition

This Initiative undertaken by ISHNE was prompted by several factors. Interest to ARVC/D as a cause of sudden death, particularly in the young, is growing and cascade screening of family members to ARVC/D patients has become a widely spread clinical routine. Because of uncertainty in interpretation of genetic screening results in a large number of ARVC/D patients,[19, 20] genotyping results often cannot be used to rule out ARVC/D in a family member, which makes the results of clinical evaluation decisive for ARVC/D diagnosis. In this context, epsilon wave plays a particularly important role since its positive identification leads to establishing definite ARVC/D diagnosis using the 2010 TFC. An asymptomatic first-degree mutation-positive relative to a patient with ARVC/D can therefore be diagnosed with definite ARVC/D in the absence of imaging abnormalities and otherwise normal ECG if the attending physician interprets fractionation of the terminal part of the QRS-complex (such as in Figure 3) as fulfilling epsilon wave definition.

Having such a high impact on the ARVC/D diagnosis, epsilon wave remains a qualitative criterion without quantitative assessment, which leaves room for subjective interpretation. Variability in epsilon wave assessment may have not only therapeutic implications for individuals inappropriately diagnosed with ARVC/D, as exemplified above, but also have medico-legal consequences for insurance issues, professional career and sports participation.

Epsilon wave: disease manifestation or a diagnostic criterion?

Our findings demonstrate that interobserver agreement in regard to the epsilon wave identification is unacceptably low. Even though the epsilon wave is a well acknowledged manifestation of ARVC/D associated with the delayed propagation of ventricular depolarization in the right ventricle, it was originally described as an extremely delayed low-amplitude signal which is distinctly separated from the QRS complex, and observed in patients with advanced late stages of the disease. This phenomenon was nearly always accompanied by T-wave inversion in right precordial leads.[10, 21, 22] ECG cases selected for the current study represent less obvious

examples of the depolarization abnormalities and illustrate the difficulties that may occur if epsilon wave is used for establishing ARVC/D diagnosis in patients with uncertain phenotype. The uncertainty with epsilon wave definition revealed in the first round of ECG reading could not be avoided by an attempt to specify terminology used in the definition of epsilon wave location in regard to the end of the QRS complex. Our results suggest that, using its current definition,[1] the epsilon wave may represent a caveat when used as a diagnostic criterion and may lead to overdiagnosing ARVC/D in patients, who do not fulfill diagnostic criteria for ARVC/D otherwise.

Association with other ECG abnormalities

It is possible that other clinical characteristics may be useful in establishing the presence of the epsilon wave, such as their association with T-wave inversions in the same leads or positive ventricular late potentials.[18] While the later remains to be proven in larger patient cohorts, common coexistence of epsilon waves with T-wave inversions have been observed repeatedly,[10, 16, 18, 21-23] is noted in the majority of ECG-patterns classified as epsilon waves in our study, and reported in 89% of patients with epsilon waves in the pooled registry dataset.

Being a late manifestation of the disease, appearance of the epsilon wave is preceded by localized prolongation of QRS complex in the right precordial leads,[16] which has been defined as prolonged TAD, which according to the 2010 TFC document fulfills a minor diagnostic criterion when it is equal or exceeds 55 ms.[1] Figure 7 represents an example of longitudinal changes in the appearance of the ventricular depolarization abnormality over the ten years period. In the pooled registry dataset, all 105 patients with definite ARVC/D and positively identified epsilon wave also fulfilled the prolonged TAD-criterion. The writing group therefore suggests that depolarization abnormalities in the right precordial leads should not be interpreted as an epsilon wave if TAD ≥55ms is not fulfilled.

Even though interobserver agreement in epsilon wave definition demonstrated in our study was low, pooled registry data analysis suggests that appearance of epsilon wave as an isolated finding without other clinical features suggestive of ARVC/D is highly unlikely.

Conclusion

Interobserver variability in assessment of epsilon wave performed by principal investigators of several large international ARVC/D registries is high. However the relative impact of epsilon wave on the diagnosis in ARVC/D patients represented in the participating registries is negligibly low as patients are unlikely to express epsilon wave as an isolated finding and in the vast majority of patients it is accompanied by other clinical manifestations that are sufficient for a definite ARVC/D diagnosis.

The results of our survey question the value of epsilon wave for ARVC/D diagnosis and urge to extreme caution in assessment of the epsilon wave presence, especially in patients or individuals undergoing presymptomatic screening who would not fulfill diagnostic criteria otherwise. An isolated epsilon wave should therefore not be considered as a major criterion in cases when the only other finding is positive family history for ARVC/D.

Funding sources

The study was supported by The Swedish Heart-Lung Foundation.

Disclosures

None relevant.

References

1. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121:1533-41.
2. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G and Camerini F. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *British heart journal*. 1994;71:215-8.
3. Fontaine G, Guiraudon G, Frank R, Vedel J, Grosgogeat Y, Cabrol C and Facquet J. Simulation studies and epicardial mapping in ventricular tachycardia: study of mechanisms and selection for surgery. In: H. E. Kulbertus, ed. *Reentrant Arrhythmias* Lancaster: MTP Pub; 1977: 334-350.
4. Fontaine G and Chen HS. Arrhythmogenic right ventricular dysplasia back in force. *Am J Cardiol*. 2014;113:1735-9.
5. Marcus FI. Electrocardiographic features of inherited diseases that predispose to the development of cardiac arrhythmias, long QT syndrome, arrhythmogenic right ventricular cardiomyopathy/dysplasia, and Brugada syndrome. *J Electrocardiol*. 2000;33 Suppl:1-10.
6. Steriotis AK, Bauce B, Daliento L, Rigato I, Mazzotti E, Folino AF, Marra MP, Brugnaro L and Nava A. Electrocardiographic pattern in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol*. 2009;103:1302-8.
7. Marcus FI and Abidov A. Arrhythmogenic Right Ventricular Cardiomyopathy 2012: Diagnostic Challenges and Treatment. *J Cardiovasc Electrophysiol*. 2012.

8. You CC, Tseng YT and Hsieh MH. An epsilon wave in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Int J Cardiol*. 2007;119:e63-4.
9. Nasir K, Bomma C, Tandri H, Roguin A, Dalal D, Prakasa K, Tichnell C, James C, Spevak PJ, Marcus F and Calkins H. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. *Circulation*. 2004;110:1527-34.
10. Fontaine G, Fontaliran F, Hebert JL, Chemla D, Zenati O, Lecarpentier Y and Frank R. Arrhythmogenic right ventricular dysplasia. *Annu Rev Med*. 1999;50:17-35.
11. Quarta G, Ward D, Tome Esteban MT, Pantazis A, Elliott PM, Volpe M, Autore C and McKenna WJ. Dynamic electrocardiographic changes in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart*. 2010;96:516-22.
12. Gottschalk B, Gysel M, Barbosa-Barros R, De Sousa Rocha RP, Perez-Riera AR, Zhang L, Fontaine G and Baranchuk A. The use of fontaine leads in the diagnosis of arrhythmogenic right ventricular dysplasia. *Ann Noninvasive Electrocardiol*. 2014;19:279-84.
13. Peters S and Trummel M. Diagnosis of arrhythmogenic right ventricular dysplasia-cardiomyopathy: value of standard ECG revisited. *Ann Noninvasive Electrocardiol*. 2003;8:238-45.
14. Kenigsberg DN, Kalahasty G, Grizzard JD, Wood MA and Ellenbogen KA. Images in cardiovascular medicine. Intracardiac correlate of the epsilon wave in a patient with arrhythmogenic right ventricular dysplasia. *Circulation*. 2007;115:e538-9.
15. Wang J, Yang B, Chen H, Ju W, Chen K, Zhang F, Cao K and Chen M. Epsilon waves detected by various electrocardiographic recording methods: in patients with arrhythmogenic right ventricular cardiomyopathy. *Tex Heart Inst J*. 2010;37:405-11.

16. Kies P, Bootsma M, Bax JJ, Zeppenfeld K, van Erven L, Wijffels MC, van der Wall EE and Schalij MJ. Serial reevaluation for ARVD/C is indicated in patients presenting with left bundle branch block ventricular tachycardia and minor ECG abnormalities. *J Cardiovasc Electrophysiol*. 2006;17:586-93.
17. Borgquist R, Haugaa KH, Gilljam T, Bundgaard H, Hansen J, Eschen O, Jensen HK, Holst AG, Edvardsen T, Svendsen JH and Platonov PG. The diagnostic performance of imaging methods in ARVC using the 2010 Task Force criteria. *European heart journal cardiovascular Imaging*. 2014;15:1219-25.
18. Alter P and Grimm W. Pronounced epsilon waves in arrhythmogenic right ventricular dysplasia. *J Cardiovasc Electrophysiol*. 2004;15:248.
19. Andreasen C, Nielsen JB, Refsgaard L, Holst AG, Christensen AH, Andreasen L, Sajadieh A, Haunso S, Svendsen JH and Olesen MS. New population-based exome data are questioning the pathogenicity of previously cardiomyopathy-associated genetic variants. *Eur J Hum Genet*. 2013;21:918-28.
20. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). *Heart Rhythm*. 2011;8:1308-39.
21. Jaoude SA, Leclercq JF and Coumel P. Progressive ECG changes in arrhythmogenic right ventricular disease. Evidence for an evolving disease. *Eur Heart J*. 1996;17:1717-22.
22. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C and Grosgogeat Y. Right ventricular dysplasia: a report of 24 adult cases. *Circulation*. 1982;65:384-98.

23. Sajeev CG, Jayakumar TG, Krishnan MN and Venugopal K. Epsilon wave. *Int J Cardiol*. 2004;93:315.

Clinical Perspectives

Being a major diagnostic criterion in the context of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), epsilon wave has great impact on the diagnostic score, which can be pivotal in patients with minimal clinical manifestations of the disease or family members undergoing screening for ARVC/D. However, it remains not quantifiable and therefore may leave room for substantial subjective interpretation. The results of our study demonstrate that even among ARVC/D experts, that there is unacceptably high interobserver variability in the interpretation of whether an epsilon wave is present or absent. The results of this study also showed that presence or absence of an episilon wave has little impact on diagnosis of ARVC/D in experienced centers. This reflects the fact that epsilon waves, when present, are late manifestations of the disease. As a result, the diagnosis of ARVC/D in these individuals can be determined based on other 2010 Task Force criteria. ARVC/D patients are very unlikely to express an epsilon wave as an isolated finding and as noted above when present is accompanied by other clinical manifestations that are sufficient for a definite ARVC/D diagnosis. Our findings urge extreme caution in interpretation of ECG patterns in individuals assessed for ARVC/D and suggest that an isolated epsilon wave should not be a major criterion in cases when the only other finding is family history. Implementation of our study findings in clinical practice is likely to improve accuracy of ARVC/D diagnostics using the revised 2010 Task Force criteria and reduce the risk of inappropriate ARVC/D diagnosis.

Figure legends

Figure 1: ECG reading results by individual panel members (R1-R7). Each line corresponds to one ECG pattern. Shadowed cells indicate the pattern being recognized as epsilon wave by individual panel member. The line at the bottom indicates the total number of ECG patterns recognized as epsilon waves per reviewer.

Figure 2: ECG patterns classified as epsilon waves by all (panels A and B) or majority (at least 6) reviewers (panels C and D)

Figure 3: ECG patterns unanimously considered as not fulfilling epsilon wave definition

Figure 4: ECG patterns for which no agreement could be reached, i.e. they were recognized as epsilon waves by 4 of 7 panelists

Figure 5: Similar ECG patterns with a notch after the end of QRS complex in lead V_1 that have been judged differently depending on the notch location in regard to the global end of QRS complex estimated from available right precordial leads. Numbers under the ECG tracings indicate the number of panelists who positively identified the ECG patterns as epsilon waves

Figure 6: Assessment of epsilon wave importance for ARVC/D diagnosis from the pooled dataset of 105 ARVC/D patients with epsilon waves out of 815 definite ARVC/D patients from five large ARVC/D registries (see Table 1 for details). Exclusion of the major and minor depolarization criteria from the diagnostic score would not affect definite diagnostic category in 95 patients (90%). Of the 10 patients who would loose their definite ARVC/D diagnostic category, nine still have TAD-criterion positive and therefore would still fulfill diagnostic criteria for ARVC/D. In total, only one of 105 patients with epsilon-waves had ARVC/D diagnosis dependent on the epsilon-wave presence.

Figure 7: Progression of ventricular depolarization abnormality in a patient with ARVC/D over ten years follow-up. It is first seen as a fractionation of the terminal part of QRS-complex with prolonged TAD (1989) but ten years later appears as a very distinct

epsilon-wave observed in all chest leads with particularly high amplitude in leads V_1-V_3.

(*Courtesy of Anneli Svensson)*

Table 1: Epsilon wave prevalence among patients with definite ARVC/D in the European/American registries

	Definite ARVC/D by TF2010	Patients with epsilon wave present	Prevalence of epsilon wave
Johns Hopkins	308	28	9%
Nordic	236	40	17%
Italian	147	14	10%
Swiss	89	22	25%
North-American	108	1	0,9%
TOTAL	**815**	**105**	**13%**

Figure 1

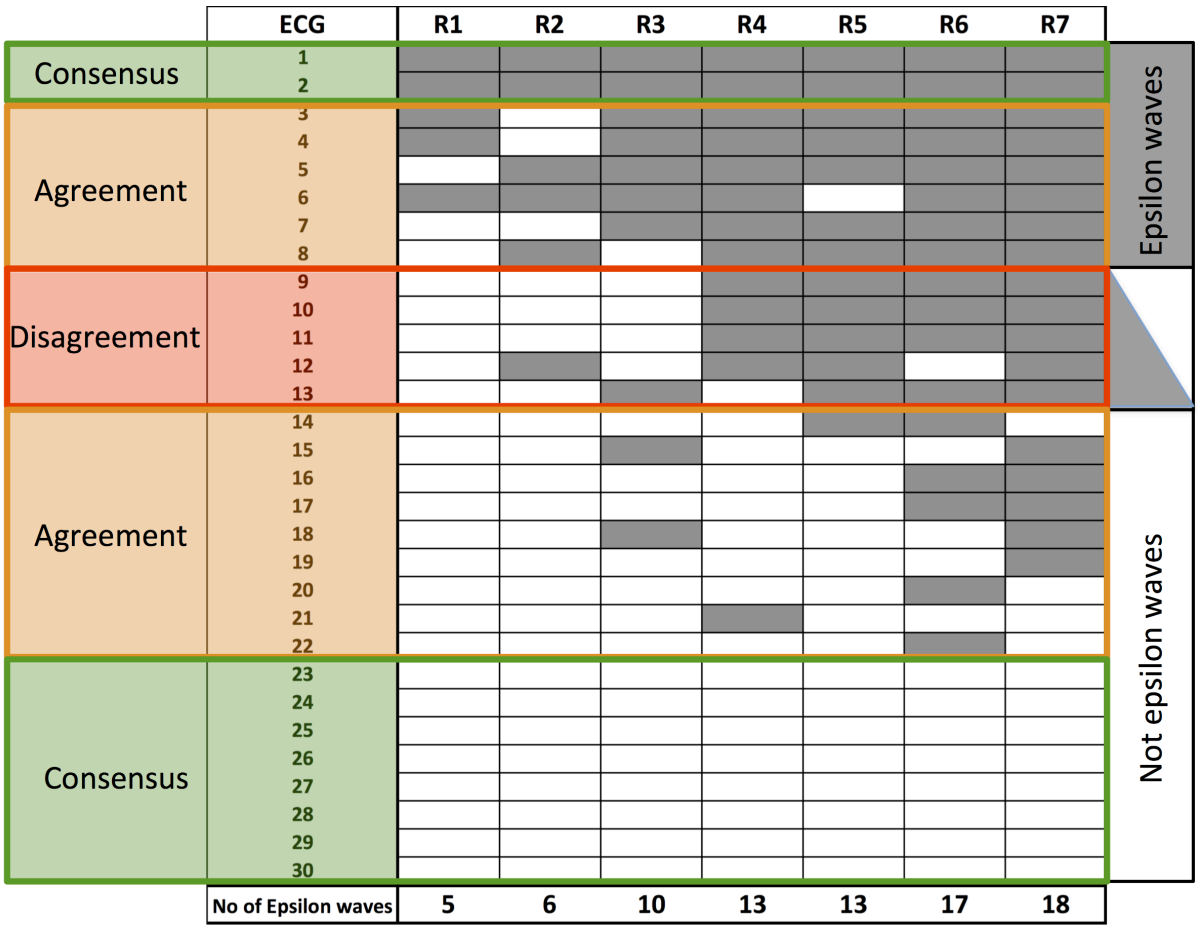
ECG
R1
R2
R3
R4
R5
R6
R7
Consensus
Agreement
Disagreement
Agreement
Consensus
Epsilon waves
Not epsilon waves
No of Epsilon waves
5
6
10
13
13
17
18

Figure 2:

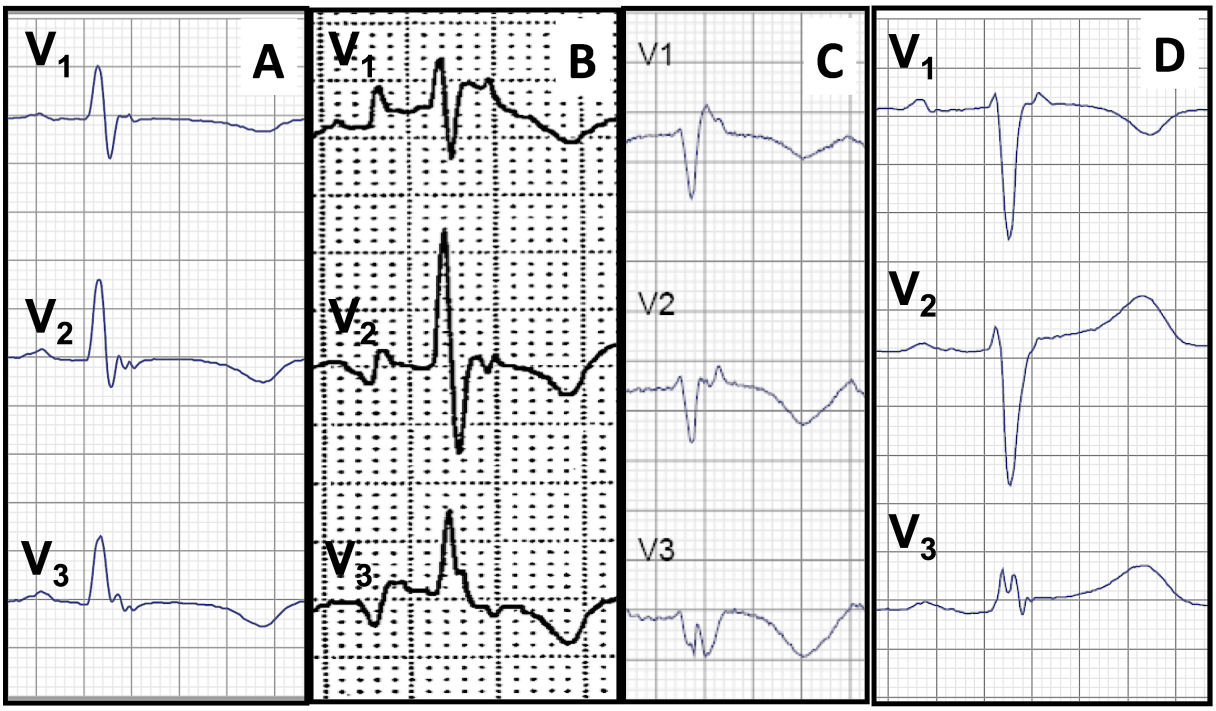

Figure 3:

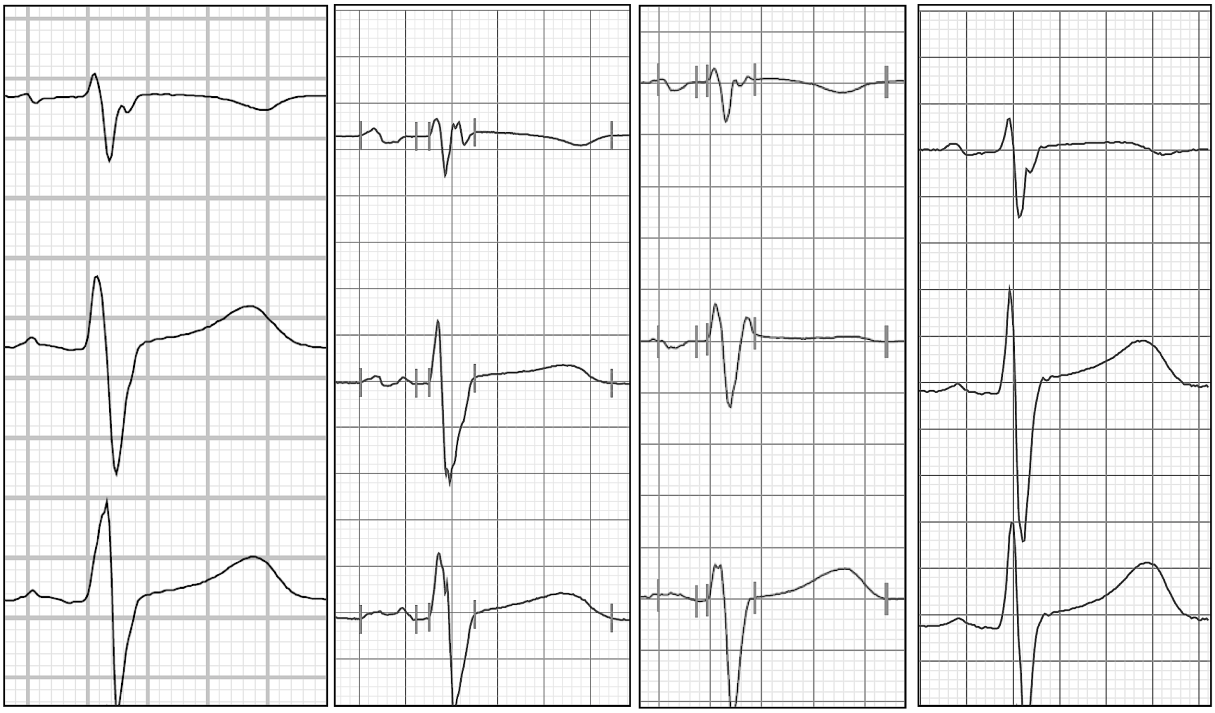

Figure 4:

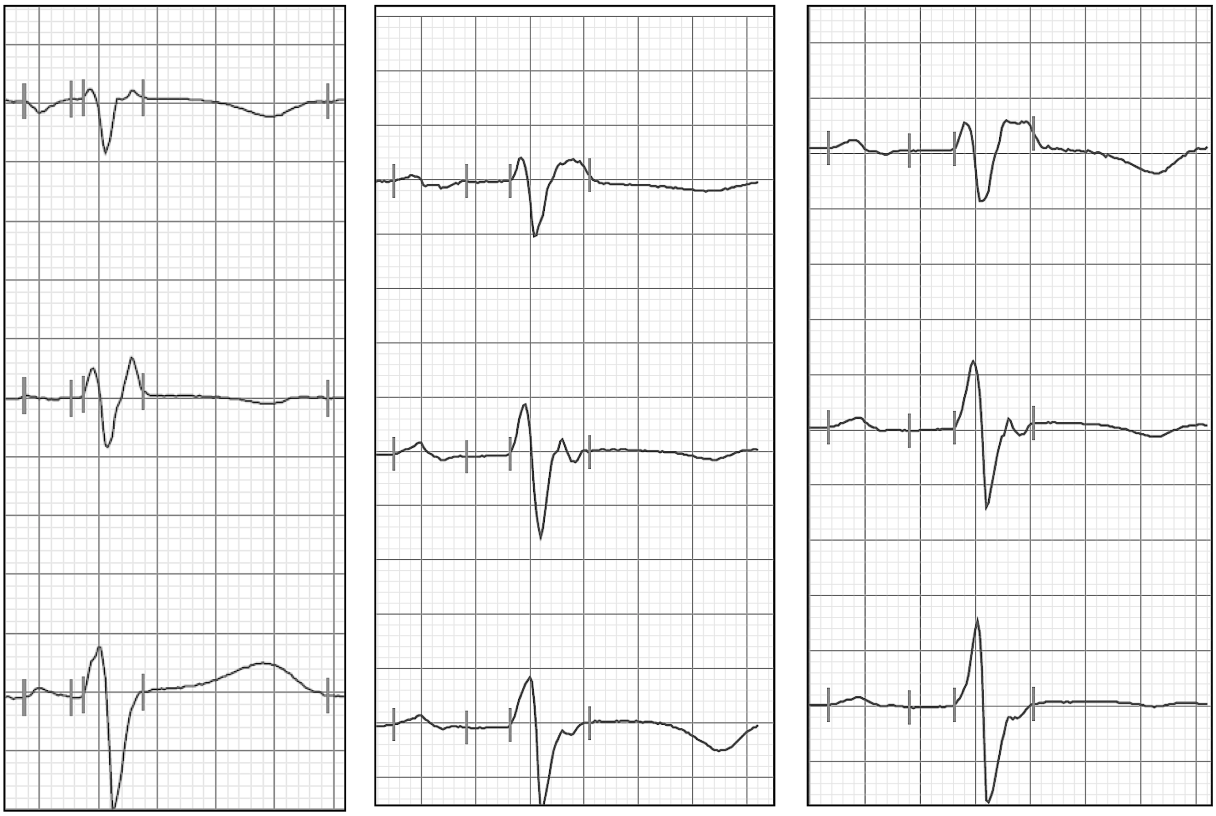

Figure 5:

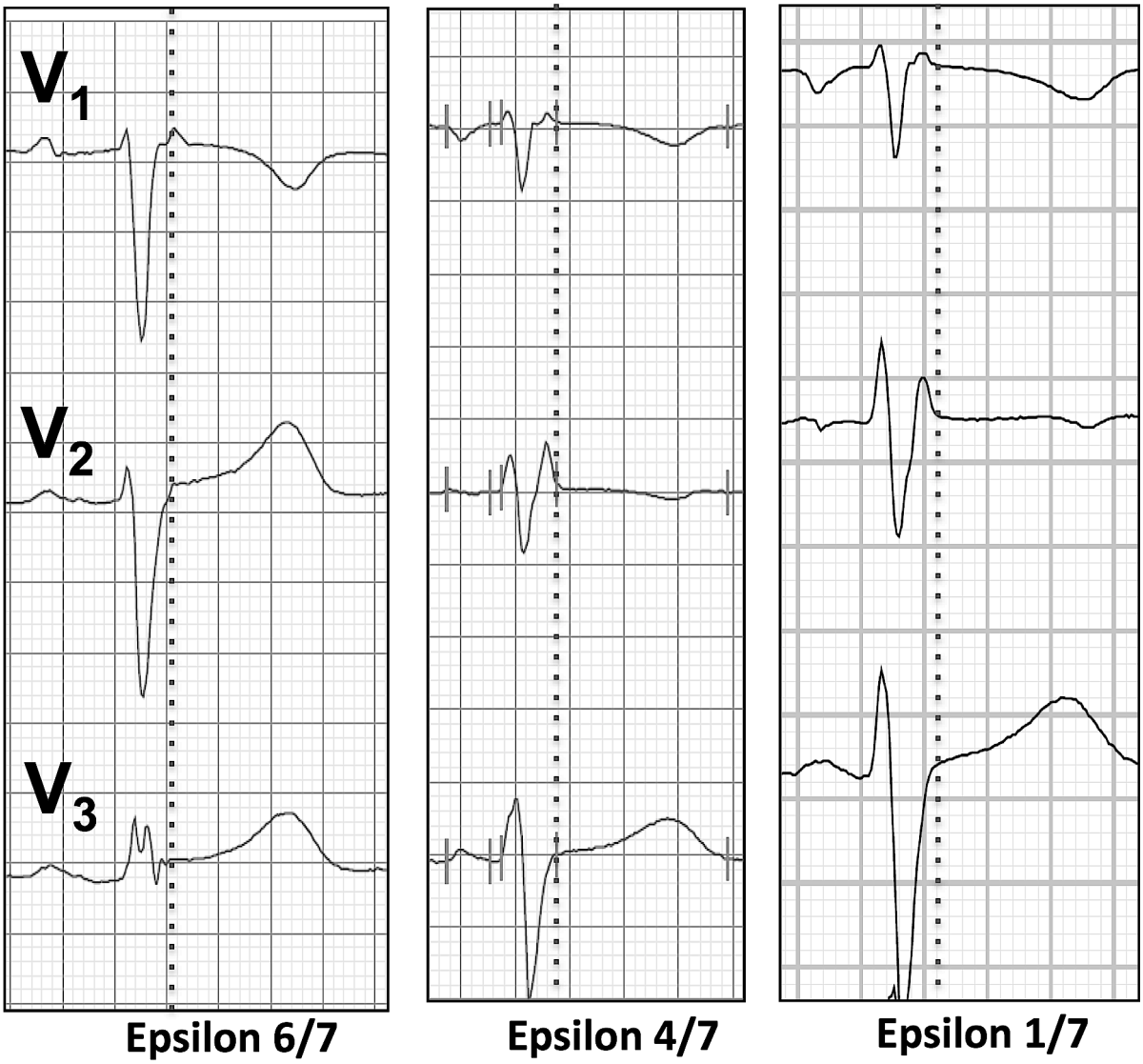

Figure 6:

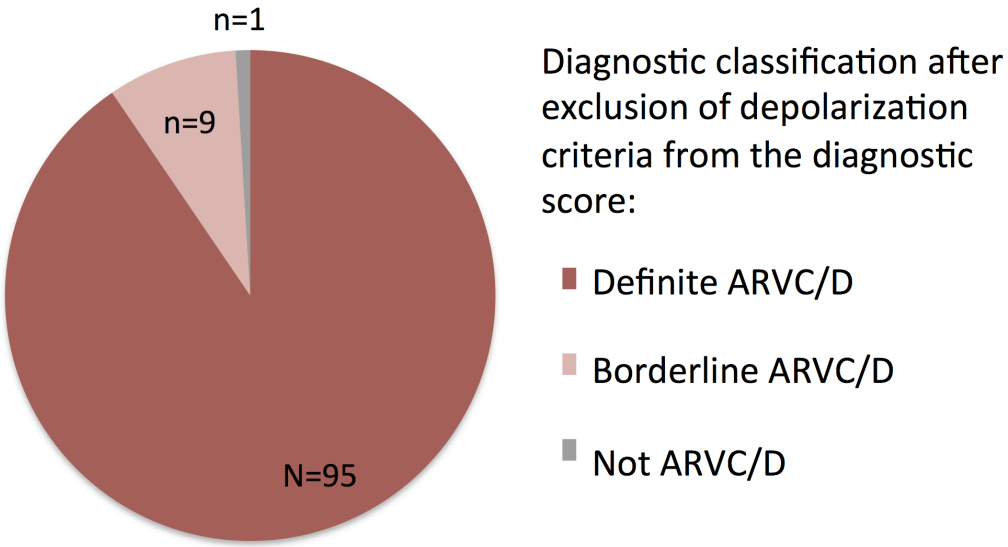
n=1
n=9
N=95
Diagnostic classification after exclusion of depolarization criteria from the diagnostic score:
Definite ARVC/D
Borderline ARVC/D
Not ARVC/D

Figure 7: