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Diagnosing arrhythmogenic right ventricular cardiomyopathy by 2010 Task Force Criteria: clinical performance and simplified practical implementation

Laurens P. Bosman[1,2†], Julia Cadrin-Tourigny [3†], Mimount Bourfiss [2], Mounes Aliyari Ghasabeh[4], Apurva Sharma[5], Crystal Tichnell[5], Rob W. Roudijk [1,2], Brittney Murray [5], Harikrishna Tandri[5], Paul Khairy [3], Ihab R. Kamel[4], Stefan L. Zimmerman[4], Johannes B. Reitsma[6], Folkert W. Asselbergs [1,2,7,8], J. Peter van Tintelen [1,9], Jeroen F. van der Heijden[2], Richard N.W. Hauer[1,2], Hugh Calkins [5], Cynthia A. James[5†], and Anneline S.J.M. te Riele [1,2*†]

[1]Netherlands Heart Institute, Moreelsepark 1, 3511 EP Utrecht, the Netherlands; [2]Division of Heart and Lungs, Department of Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; [3]Department of Medicine, Montreal Heart Institute, University of Montreal, Montreal, Canada; [4]Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins Hospital, Baltimore, MD, USA; [5]Division of Cardiology, Department of Medicine, Johns Hopkins Hospital, Baltimore, MD, USA; [6]Department of Epidemiology, Julius Center, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; [7]Faculty of Population Health Sciences, Institute of Cardiovascular Science, University College London, London, UK; [8]Health Data Research UK and Institute of Health Informatics, University College London, London, UK; and [9]Department of Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

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Aims Arrhythmogenic right ventricular cardiomyopathy (ARVC) is diagnosed by a complex set of clinical tests as per 2010 Task Force Criteria (TFC). Avoiding misdiagnosis is crucial to prevent sudden cardiac death as well as unnecessary implantable cardioverter-defibrillator implantations. This study aims to validate the overall performance of the TFC in a real-world cohort of patients referred for ARVC evaluation.

Methods and results We included patients consecutively referred to our centres for ARVC evaluation. Patients were diagnosed by consensus of three independent clinical experts. Using this as a reference standard, diagnostic performance was measured for each individual criterion as well as the overall TFC classification. Of 407 evaluated patients (age 38 ± 17 years, 51% male), the expert panel diagnosed 66 (16%) with ARVC. The clinically observed TFC was false negative in 7/66 (11%) patients and false positive in 10/69 (14%) patients. Idiopathic outflow tract ventricular tachycardia was the most common alternative diagnosis. While the TFC performed well overall (sensitivity and specificity 92%), signal-averaged electrocardiogram (SAECG, $P = 0.43$), and several family history criteria ($P \geq 0.17$) failed to discriminate. Eliminating these criteria reduced false positives without increasing false negatives (net reclassification improvement 4.3%, $P = 0.019$). Furthermore, all ARVC patients met at least one electrocardiogram (ECG) or arrhythmia criterion (sensitivity 100%).

Conclusion The TFC perform well but are complex and can lead to misdiagnosis. Simplification by eliminating SAECG and several family history criteria improves diagnostic accuracy. Arrhythmogenic right ventricular cardiomyopathy can be

* Corresponding author. Tel: +31 (0)88 23 33 600. *E-mail address:* ariele3@umcutrecht.nl

† The first and last two authors shared first/last authorship.

ruled out using ECG and arrhythmia criteria alone, hence these tests may serve as a first-line screening strategy among at-risk individuals.

Keywords Arrhythmogenic right ventricular cardiomyopathy • Diagnosis • Ventricular arrhythmia • Cardiomyopathy

What's new?

- Because the 2010 Task Force Criteria (TFC) are complex, Arrhythmogenic right ventricular cardiomyopathy (ARVC) diagnosis is labour-intensive and error-prone; however, this study reveals that simplification of the TFC improves diagnostic accuracy.
- Signal-averaged electrocardiogram ($P = 0.43$) and several of the family history criteria ($P \geq 0.17$) did not significantly contribute to diagnose ARVC.
- Based on our results, the relative weight of individual major and minor criteria as well as the different categories may not be as equal as currently assumed.
- Arrhythmogenic right ventricular cardiomyopathy can be ruled out using electrocardiogram and arrhythmia criteria alone, hence these tests may serve as a first-line screening strategy, especially in relatives and mutation carriers who are often screened at regular intervals.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterized by fibrofatty myocardial replacement, predisposing patients to life-threatening ventricular arrhythmias, and progressive ventricular dysfunction.[1] Diagnosis of ARVC has major implications for affected patients and their relatives and may include lifestyle interventions, medication, and/or implantation of an implantable cardioverter-defibrillator.[2] However, the clinical manifestation of ARVC is highly variable, and accurate diagnosis of ARVC can pose a challenge to the managing physician.

The pathological gold standard for ARVC diagnosis is histological detection of fibrofatty replacement at autopsy or surgery.[3] However, due to the segmental nature of disease, histological evaluation has low sensitivity, while myocardial biopsy is an invasive procedure with inherent risks. In order to overcome these limitations, a composite reference standard was created in 1994 and modified in 2010 by an international task force.[3,4] These 'Task Force Criteria' (TFC) consist of consensus-based criteria in structural, histological, electrocardiographic, arrhythmic, and familial features of the disease, and serve as the clinical standard for ARVC diagnosis.

While the TFC provide a uniform definition of ARVC that guides clinical practice and scientific research, a complete diagnostic workup as per TFC is complex and time-consuming. Furthermore, the TFC is consensus-based and derived by comparison of severely affected ARVC patients to healthy controls,[4] thereby potentially overestimating its diagnostic value compared with the real-world clinical setting. Although prior studies have attempted to determine the diagnostic value of individual criteria for ARVC,[4–7] the TFC as a whole have never been validated in an independent patient cohort. Therefore, this study aims to validate the diagnostic performance of (i) individual and (ii) composite TFC in a large real-world cohort of patients referred for ARVC evaluation.

Methods

Study population

We included consecutive patients referred to our hospitals [UMC Utrecht (UMCU), the Netherlands and Johns Hopkins Hospital (JHH), Baltimore, USA] for diagnostic ARVC evaluation between 2009 and 2011 including cardiovascular magnetic resonance (CMR) imaging. The study was approved by the local institutional ethics review boards.

Data collection

All patients received clinical diagnostic evaluation upon discretion of the managing physician. Data were retrospectively collected from medical records and included clinical history and test results according to the standards and definitions of the TFC, including electrocardiograms (ECGs), signal-averaged electrocardiograms (SAECGs), Holter recordings, CMR imaging, echocardiography, ventricular cine-angiography, genetic testing, three-generation pedigrees, and endomyocardial biopsies. In addition, results from other clinically relevant diagnostic tests (e.g. coronary angiograms, exercise stress tests and electrophysiology study) were collected when available.

Diagnostic classification

Two diagnostic classifications of ARVC were used. First, patients were classified per TFC, which consist of major (2 points) and minor (1 point) criteria across six categories.[4] Within each category, a patient can fulfil a major, minor, or no criterion. Patients are classified as 'definite ARVC' when the combined score over all categories is ≥4 points. Implicit to this classification score is the assumption that all minor and all major criteria within the same category are of equal diagnostic value; and that all six categories have equal diagnostic weight.

Second, in order to validate the diagnostic accuracy of the TFC, the consensus of a panel of ARVC experts was used as a reference standard. This approach is consistent with international Task Force recommendations, which consider the proposed TFC to be a 'working framework to improve the diagnosis and management of this condition', while advocating for the totality of evidence to be considered on an individualized basis.[4] Prior studies have selected a reference population of ARVC patients that fulfilled diagnostic criteria independent of the criterion under investigation;[4,7] however, this method may potentially introduce bias.[8] Applying an expert panel is a recommended approach to test validity of diagnostic algorithms in the absence of a single diagnostic gold standard.[9,10]

The expert panel protocol was designed in accordance with recommendations

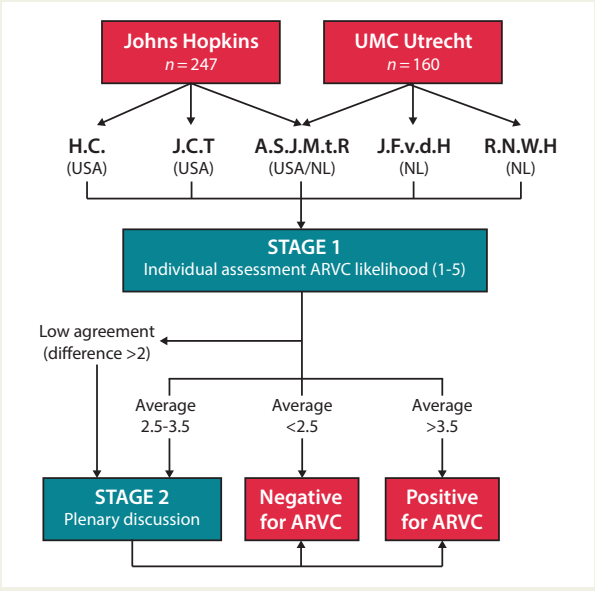

Figure 1 Flowchart of the expert panel protocol. A staged decision-making process was utilized, in which every expert independently scored presence or absence of ARVC for every patient on a scale from 1 to 5. Patients with disagreement (>2 scale steps difference) or unclear diagnosis (average 2.5–3.5) were discussed in a plenary session to obtain final consensus classification. ARVC, arrhythmogenic right ventricular cardiomyopathy; UMC, University Medical Centre.

(*Figure 1*).[9,11] The two panels, one in each hospital, consisted of three physicians specialized in ARVC [R.N.W.H., J.F.v.d.H., and A.S.J.M.t.R. (UMCU) and H.C., J.C.T., and A.S.J.M.t.R. (JHH)]. First, each panel member evaluated the patients independently based on a standardized presentation of all available diagnostic information. To ensure the best possible diagnostic classification, experts were asked to re-evaluate all available information (with the possibility to overrule initial clinical assessments) including a re-review of CMR images by two expert radiologists specialized in ARVC (I.R.K. and S.L.Z.). Using this information, the panel members scored the likelihood of ARVC diagnosis for each subject on a five-step scale: (i) definitely not, (ii) not likely, (iii) possible, (iv) likely, and (v) definitely ARVC. In case of disagreement (defined as >2 scale-step difference between two experts) or unclear diagnosis (defined as an overall average of 2.5–3.5), cases were discussed in a plenary session to reach consensus. After the initial classification by the expert panel, follow-up data [3.6 (0.3–6.3) years] was reviewed as an additional source of information to validate the initial diagnostic classification. The performance of the expert panel was evaluated by inter- and intra-observer agreement, calculated with Cohen's kappa statistic. To estimate intra-observer agreement, a stratified blinded random sample of 15 cases was re-evaluated 4–8 months after initial classification.

Data analysis

Data analysis was performed in RStudio version 1.1.414 (Boston, MA, USA). Continuous variables were compared using the *t*-test or Mann–Whitney *U* test as appropriate, and categorical variables using the χ^2 or Fisher's exact tests. Patterns of missing data were evaluated and assumed to be missing at random. Missing values were replaced using multiple imputations by chained equations based on all collected variables and the expert panel diagnosis to create 100 imputed datasets.[12] All analyses were repeated in every imputed dataset separately, and results were pooled using Rubin's rules.[13] To determine diagnostic values that reflect real-world clinical practice, data from original clinical test interpretations was analysed as opposed to expert reviews, which were solely used to obtain the best possible diagnostic classification. Using the panel diagnosis as a reference, the diagnostic TFC performance was evaluated by analysis of test characteristics (i.e. sensitivity, specificity) and logistic regression with Firth bias correction to accommodate for the low numbers of events for certain predictors.[14] In addition, the Youden's index [(false positive rate) + (false negative rate) − 1][15] was calculated to assess overall diagnostic value: Youden's index ranges from 0 to 1, with 1 indicating a test with 100% sensitivity and specificity. Overall classification performance was compared with the net reclassification improvement. To estimate the relative weights of the diagnostic contribution of different categories of criteria, multivariable logistic regression was used and results were internally validated by bootstrapping. Two-tailed *P*-values <0.05 were considered statistically significant.

Results

Study population

The study population included 407 patients who were evaluated for ARVC at UMCU or JHH. Baseline characteristics are presented in *Table 1*. Half (51%) of the population was male and mean age was 38 ± 17 years. Clinical evaluation was performed because of symptoms/abnormal test results in 261 (63%) patients and because of family history in the remaining 146 (37%) patients. Symptoms for which patients were referred included palpitations ($n = 88$, 34%), symptomatic ventricular tachycardia (VT), ventricular fibrillation (VF), or sudden cardiac arrest (SCA) ($n = 51$, 20%), (pre-)syncope ($n = 49$, 19%), dyspnoea ($n = 18$, 7%), and chest pain ($n = 17$, 7%). Although all patients were referred for CMR evaluation of ARVC, CMR results of seven (2%) patients were excluded due to imaging artefacts. Extended and stratified versions of the baseline table is available in Supplementary material online, *Tables S1–S3*, and a complete list of pathogenic mutations in Supplementary material online, *Table S4*.

Expert panel diagnosis and clinical Task Force Criteria score

In total, 66 (16%) patients were diagnosed with ARVC by the expert panel, with an excellent level of agreement ($K \geq 0.81$) and intra-observer reproducibility ($K \geq 0.85$) (Supplementary material online, *Table S5*). *Figure 2* shows the results of the expert panel evaluation vs. the TFC score. Using the expert panel as a reference, 7/66 (11%) patients with ARVC were not detected by the TFC (i.e. false negatives), while 10/69 (14%) of patients fulfilling TFC did not have ARVC (i.e. false positives) (Supplementary material online, *Table S6A* and *B*). The most common alternative diagnosis of patients meeting TFC was idiopathic right ventricular (RV) outflow tract VT or premature ventricular complexes (PVCs) (Supplementary material online, *Figure S1*). After reviewing the information from 3.6 (0.3–6.3) years of follow-up, six cases (1.5%) received a different classification at last follow-up: all were cases classified as at risk of ARVC who developed definite ARVC during follow-up, confirming their initial 'at-risk' classification (Supplementary material online, *Figure S2*).

Table 1 Clinical characteristics

		Overall (*n* = 407)	Not ARVC (*n* = 341)	ARVC (*n* = 66)	*P*-value
Male sex		206 (51)	175 (51)	31 (47)	0.608
Age (years)		38 ± 17	37 ± 17	40 ± 14	0.245
Indication					
Symptomatic/abnormal test		261 (64)	219 (64)	42 (64)	1.000
Family screening		146 (36)	122 (36)	24 (36)	
TFC score		2 (1–3)	1 (1–2)	5 (4–6)	<0.001
I. Structural					
Echocardiography (*n* = 315)	Major	12 (4)	2 (1)	10 (20)	<0.001
	Minor	8 (3)	5 (2)	3 (6)	
CMR (*n* = 400)	Major	53 (13)	25 (7)	28 (45)	<0.001
	Minor	30 (8)	15 (4)	15 (24)	
RV cine-angiography (*n* = 41)	Major	14 (34)	3 (13)	11 (61)	0.004
II. Tissue histology					
Tissue histology (*n* = 28)	Major	2 (7)	1 (8)	1 (6)	0.669
	Minor	1 (4)	–	1 (6)	
III. Repolarization					
ECG (*n* = 398)	Major	45 (11)	7 (2)	38 (58)	<0.001
	Minor	40 (10)	32 (9)	8 (12)	
IV. Depolarization					
ECG (*n* = 398)	Major	–	–	–	<0.001
	Minor	92 (24)	56 (17)	36 (58)	
SAECG (*n* = 119)	Minor	59 (50)	46 (50)	13 (50)	1.000
V. Arrhythmia					
VT LBBB superior axis (*n* = 407)	Major	19 (5)	8 (2)	11 (17)	<0.001
VT LBBB other/unknown axis (*n* = 407)	Minor	49 (12)	27 (8)	22 (33)	<0.001
Holter monitor >500 PVC/24 h (*n* = 298)	Minor	127 (43)	78 (33)	49 (82)	<0.001
VI. Family history					
Pathogenic mutation (*n* = 190)	Major	67 (35)	31 (24)	36 (57)	<0.001
First-degree ARVC (*n* = 407)	Major	70 (18)	50 (15)	20 (30)	0.005
First-degree ARVC autopsy (*n* = 407)	Major	30 (8)	26 (8)	4 (6)	0.804
First-degree ARVC unconfirmed (*n* = 407)	Minor	5 (1)	5 (2)	–	0.689
First-degree SCD <35 years (*n* = 407)	Minor	29 (7)	24 (7)	5 (8)	1.000
Second-degree ARVC (*n* = 407)	Minor	27 (7)	26 (8)	1 (2)	0.109

ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; LBBB, left bundle branch block; PVC, premature ventricular complex; RV, right ventricular; SAECG, signal-averaged ECG; SCD, sudden cardiac death; TFC, Task Force Criteria; VT, ventricular tachycardia.

Evaluation of the individual Task Force Criteria

Of all tests included in the TFC, RV cine-angiography (available in 10%) and tissue biopsy (available in 7%) were not routinely performed and therefore excluded from further analyses. In addition, epsilon waves (0%) and T-wave inversions (TWIs) V1–4 in combination with complete right bundle branch block (cRBBB) (1%) were rarely observed, precluding further analysis. The diagnostic accuracy of the remaining individual TFC is summarized in *Figure 3*.

As can be appreciated from *Figure 3*, most individual TFC were significantly associated with ARVC diagnosis. Of note, the only criteria not significantly associated with ARVC diagnosis were late potentials on SAECG ($P = 0.43$), autopsy diagnosis in a first-degree relative ($P = 0.72$), and all minor family history criteria ($P \geq 0.17$).

As TFC in the category 'global or regional dysfunction and structural alterations' can be measured by either echocardiography or CMR, we performed a head-to-head comparison of these modalities. Compared with CMR, echocardiographic criteria were less frequently fulfilled (8% echocardiography vs. 22% CMR) which lead to a highly specific, yet poorly sensitive diagnostic yield. As such, CMR had superior diagnostic accuracy compared with echocardiography (Youden's index 0.57 and 0.25, respectively, net reclassification improvement 32%, $P < 0.001$).

Evaluation of the composite Task Force Criteria

The overall sensitivity and specificity of the composite TFC score [which was defined as fulfilment of ≥4 points (i.e. 'definite ARVC' as

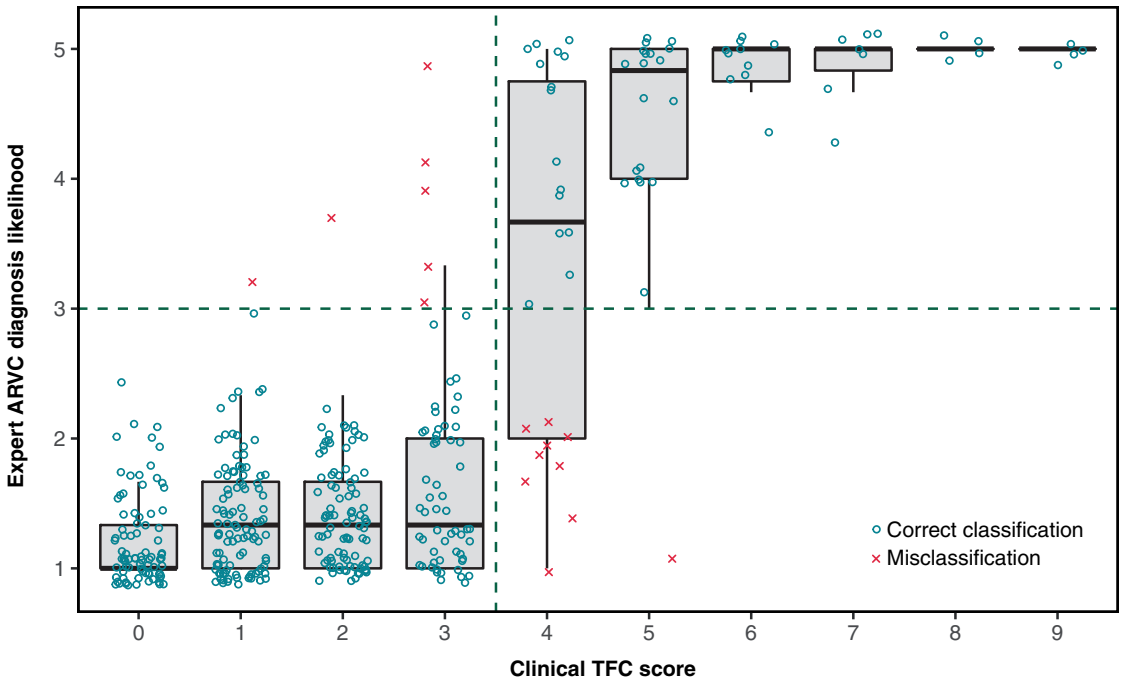

Figure 2 Expert panel score vs. clinically observed TFC score. Box plot with jitter plot (using small random jitter) overlay. Observed clinical TFC score (*X*-axis) is plotted against the average expert panel diagnosis likelihood (*Y*-axis). Dotted horizontal and vertical lines represent classification cut-off values (TFC ≥ 4; expert diagnostic likelihood > 3). Patients in the left upper (false negative) and right lower (false positive) quadrants are misclassified (red crosses). ARVC, arrhythmogenic right ventricular cardiomyopathy; TFC, Task Force Criteria.

per TFC)] were both 92% (*Figure 3*). Elimination of SAECG and family history criteria, which individually failed to discriminate, increased specificity to 97% while retaining 92% sensitivity. Comparing classification with and without these criteria showed a significant net reclassification improvement of 4.3% ($P = 0.019$), confirming an increase in diagnostic accuracy.

We subsequently set out to compare the performance of TFC categories using a multivariable logistic regression model. Results are shown in *Table 2*. As can be appreciated from the regression coefficients, diagnostic values of categories were not equal: the strongest association with ARVC diagnosis was observed for repolarization criteria and weakest association for depolarization criteria (β 2.67 and 1.23, respectively, indicating a two-fold difference of association with ARVC diagnosis). As a result, the likelihood of having ARVC varied between patients with the same overall TFC score, yet comprised of different categories (see Supplementary material online, *Table S7*).

Furthermore, as shown in *Figure 3*, the highest sensitivities of ARVC diagnosis were observed for having any ECG criterion (88%) or any arrhythmia criterion (89%). In combination, these criteria yielded a sensitivity of 100%, indicating a strong potential to rule out disease using these criteria alone.

Discussion

In absence of a single gold standard test, ARVC is diagnosed by the TFC: a composite set of major and minor criteria that were based upon comparison of ARVC patients with healthy subjects. As a result, the diagnostic performance of the TFC is likely substantially lower in a real-world clinical setting, in which patients suspected of ARVC may more closely resemble each other. In our study, we evaluated the diagnostic performance of the TFC in a consecutive cohort of patients referred for ARVC evaluation. This study has several interesting results. First, the TFC perform well but are not without risk of misdiagnosis. Second, the risk of misdiagnosis can be reduced by simplification of the TFC. Third, the relative weights of individual major and minor criteria as well as different categories are not equal. Last, ECG and arrhythmia criteria alone can rule out ARVC with remarkably high sensitivity. This information may help clinicians evaluating subjects for this potentially life-threatening, yet clinically challenging disease.

Arrhythmogenic right ventricular cardiomyopathy misdiagnosis: an important clinical problem

Although the TFC are a crucial tool for ARVC diagnosis, their complexity renders ARVC diagnosis prone to misinterpretation, hence leading to misdiagnosis. This was already shown by Bomma *et al.*,[16] demonstrating that 73% of presumed ARVC patients were misdiagnosed, most commonly based on CMR misinterpretation. In our study, in which CMRs were overread by two blinded radiologists and final diagnosis was determined by a robust expert panel, 11% false negatives and 14% false positives occurred. A false positive TFC

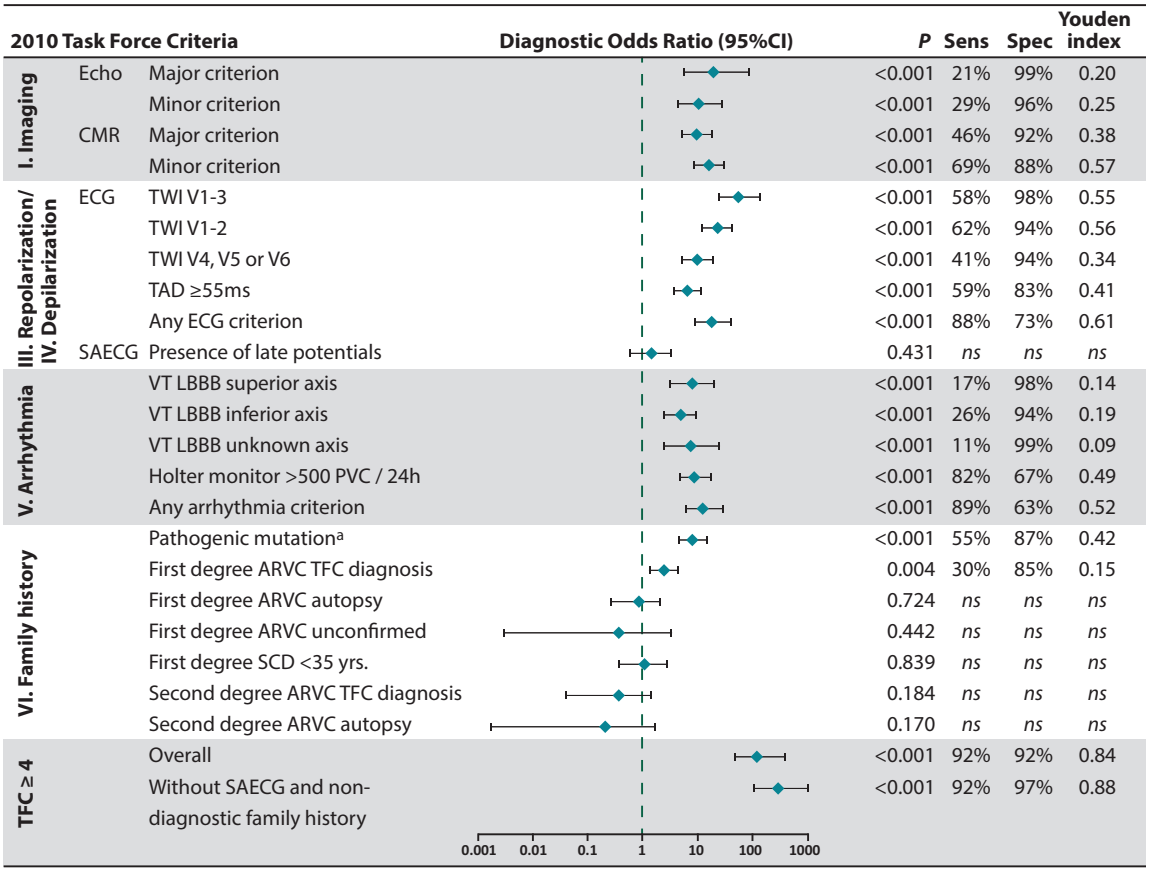

Figure 3 Diagnostic performance of individual and composite TFC. Forest plot of the diagnostic odds ratios and 95% confidence intervals. [a]Considered positive if a pathogenic or likely pathogenic variant[25] is found in ARVC-associated genes as defined by the TFC: Plakophilin-2, Desmocollin-2, Desmoglein-2, Desmoplakin, Plakoglobin, or Transmembrane protein-43. ARVC, arrhythmogenic right ventricular cardiomyopathy; CI, confidence interval; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; Echo, echocardiography; LBBB, left bundle branch block; PVC, premature ventricular complex; SAECG, signal-averaged ECG; SCD, sudden cardiac death; Sens, sensitivity; Spec, specificity; TAD, terminal activation duration; TFC, Task Force Criteria; TWI, T-wave inversion; VT, ventricular tachycardia.

classification occurred most commonly in idiopathic VT/PVC patients, which can be difficult to distinguish from ARVC.[17]

Performance of the individual Task Force Criteria

Our study reveals a significant difference in diagnostic performance of individual TFC. Results from RV cine-angiography and tissue biopsy were not included, as these tests were not routinely performed. However, with acceptable non-invasive alternatives for RV cine-angiography and questionable sensitivity of tissue biopsy,[18] the use of these invasive tests may no longer be justifiable in most situations. Also, we did not include epsilon waves and TWI V1–4 in the presence of cRBBB, as these were rarely observed. Nonetheless, the low prevalence of these criteria may itself be an indication that their contribution to ARVC diagnosis is limited. This may be explained by the fact that these signs are a late manifestation of disease.[6,19] Furthermore, the diagnostic value of the epsilon wave was recently disputed by Platonov *et al.*,[6] showing that its reproducibility is unacceptably low.

Of note, almost all other individual TFC were significantly associated with ARVC diagnosis. The highest sensitivity was observed for ECG and Holter monitoring criteria, which are indeed thought to occur early in the disease process.[20–22] Although both echocardiography and CMR criteria were significantly associated with ARVC, echocardiography had poor sensitivity and was outperformed by CMR in overall diagnostic accuracy. This is in line with the recent finding by Borgquist *et al.*,[5] showing that conventional echocardiography is unreliable to detect subtle structural changes in the right ventricle. Of note, newer techniques such as strain echocardiography (i.e. deformation imaging) may have incremental value for ARVC diagnosis, but this is not yet part of the TFC and therefore not specifically investigated in this study.

In our cohort, late potentials on SAECG were not significantly associated with ARVC diagnosis. Late potentials occurred in 50% of the ARVC cases as well as in 50% of non-ARVC cases (*Table 1*), therefore lacking both sensitivity and specificity. Other criteria not significantly associated with ARVC include autopsy diagnosis in a first-degree relative, and all minor family history criteria. For autopsy diagnosis, this

may be due to the uncertainty associated with a post-mortem ARVC diagnosis as well as limited pathologist' experience with ARVC, as previously suggested.[23] Uncertainty also exists for a first-degree relative with sudden cardiac death below the age of 35 years, which can be caused by many different entities. As for second-degree relatives, the chance of genetic predisposition is 25% (assuming the proband carries a pathogenic mutation). In combination with the incomplete penetrance of disease, the risk of ARVC may simply be too low to find a significant association in this cohort. Conversely, the presence of a pathogenic mutation confirmed by genetic analysis had the strongest diagnostic value of all family history criteria, especially high in specificity (87%), indicating its strong potential to confirm the diagnosis in patients receiving cardiologic evaluation for ARVC.

It is important to note that criteria not significantly associated with ARVC diagnosis in this study (e.g. family history and SAECG) may have better diagnostic value should they be better standardized or technologically improved. If not, they may still serve a relevant purpose such as indication for cardiologic screening or risk stratification. For example, the presence of any family history criteria provides a compelling indication for clinical evaluation, as the risk of ARVC in these relatives strongly exceeds that of the general population.

Table 2 The Task Force Criteria as a multivariable model predicting ARVC diagnosis

TFC category	Criterion fulfilment	β	SE	*P*-value
I. Structural	None/minor/major	1.54	0.36	<0.001
II. Tissue histology	–	–	–	–
III. Repolarization	None/minor/major	2.67	0.47	<0.001
IV. Depolarization	None/minor	1.23	0.72	0.088
V. Arrhythmia	None/minor/major	2.50	0.60	<0.001
VI. Family history	None/minor/major	1.73	0.41	<0.001

ARVC, arrhythmogenic right ventricular cardiomyopathy; β, regression coefficient; SE, standard error; TFC, Task Force Criteria.

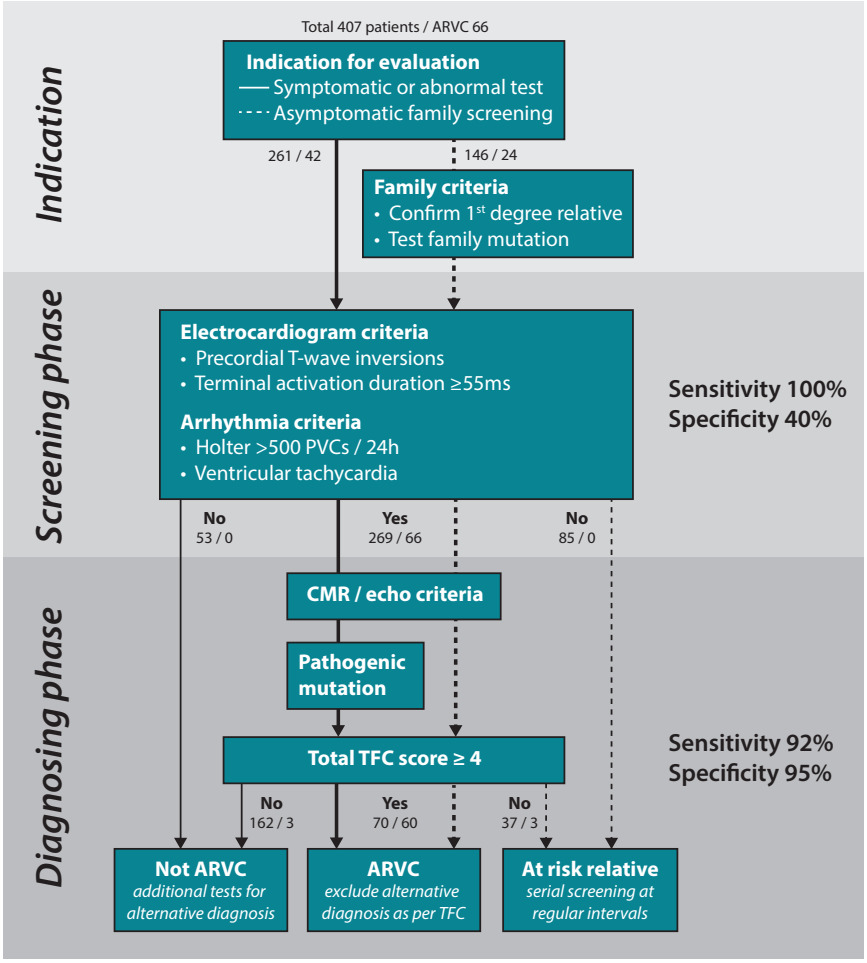

Figure 4 Simplified practical implementation of the TFC. Diagram of simplified practical implementation of the TFC, using a stepwise approach of highly sensitive ECG and arrhythmia criteria in an initial 'screening phase' to rule out ARVC. Numbers denote overall number/those with ARVC. ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; Echo, echocardiography; PVC, premature ventricular complex; TFC, Task Force Criteria.

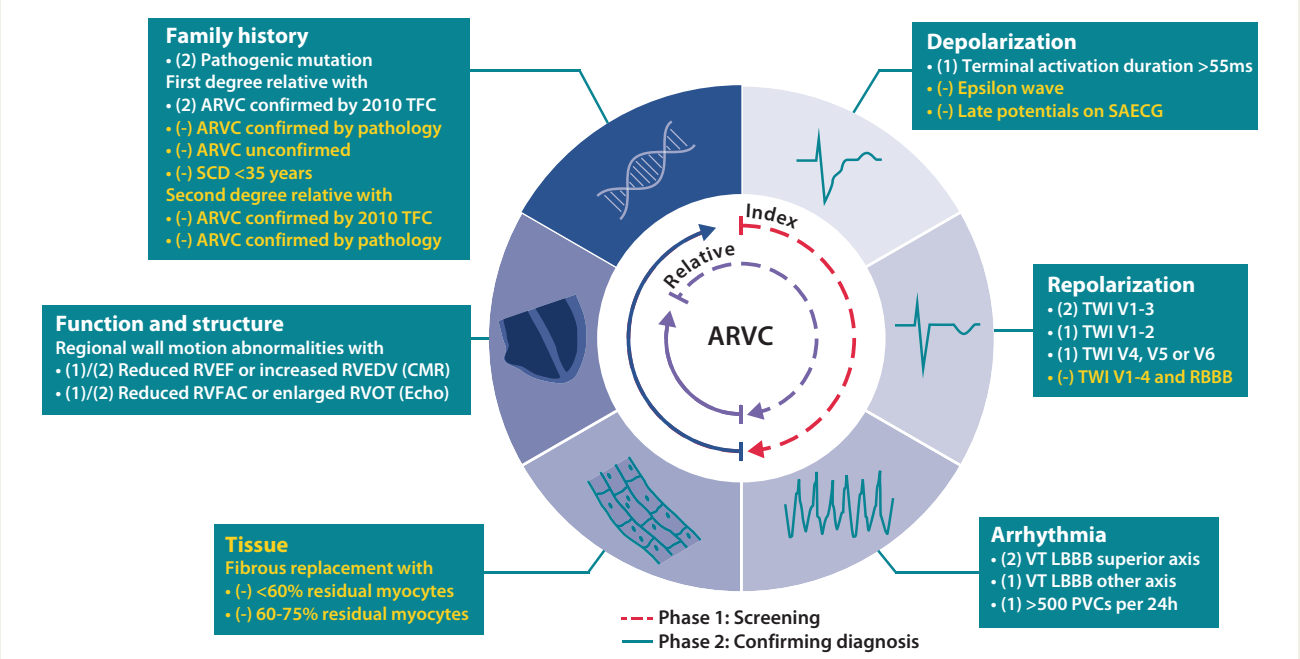

Figure 5 Overview of the TFC for diagnosing ARVC with potential simplification by eliminating several criteria (in grey). While these criteria are not required in standard diagnostic work-up for ARVC, they may still serve purpose in differential diagnosis, risk stratification, or indication for cardiologic evaluation. For relatives, the starting point should be to confirm the diagnosis of the index patient and/or genetic analysis, whereas for index patients this is the final step. (-), consider to eliminate from standard diagnostic work-up for ARVC; (1), minor criterion; (2), major criterion; ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance imaging; LBBB, left bundle branch block; PVC, premature ventricular complex; RBBB, right bundle branch block; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVFAC, right ventricular fractional area change; RVOT, right ventricular outflow tract; SAECG, signal-averaged ECG; SCD, sudden cardiac death; TFC, Task Force Criteria; TWI, T-wave inversion.

Performance of the composite Task Force Criteria

The current clinical rule for diagnosing ARVC by a TFC score of ≥4 shows overall good sensitivity and specificity of 92%. Nevertheless, the long list of criteria and modalities in the TFC make diagnosing ARVC complex and time-consuming. Our results indicate that not all criteria are required to diagnose ARVC, since they have low diagnostic accuracy and/or low prevalence. Not only does removing these criteria simplify the TFC, it may also lead to a significant improvement of its diagnostic accuracy.

Important implicative assumptions of the TFC are equality of diagnostic value of all six categories (i.e. 0–2 points per category); and equality of diagnostic value of minor (1 point) and major (2 points) criteria within the same category. If the former were true, the results from our multivariable model (*Table 2*) would have revealed similar regression coefficients, which were not the case: instead, our results indicated that some categories contribute stronger to the probability of ARVC diagnosis than others. Furthermore, as demonstrated by the analyses of the individual TFC (*Figure 3*), even the latter assumption is not justified. Overall, these results suggest an opportunity to improve TFC performance by redistribution of the relative weights ('points') attributed to each criterion.

Clinical implementation

Our study indicates that ECG and arrhythmia criteria have very high sensitivity for ARVC diagnosis, while echocardiography and CMR criteria have high specificity. This provides important information for ARVC screening and diagnosis, which need a fundamentally different, yet complimentary, approach. For screening purposes, high sensitivity is desired to not miss any affected patients. For diagnosis, high specificity is necessary to avoid a false positive diagnosis in essentially healthy individuals. Based on the results of our study, a stepwise evaluation approach may be justifiable, starting with a 'screening phase' using ECG and arrhythmia criteria to rule out ARVC, followed by a 'diagnostic phase' using imaging criteria to rule in disease. Not only would this screening phase save time and resources, most notably in serial evaluation of relatives in whom cardiac imaging may not be required for a differential diagnosis, it could also prevent false positive diagnosis by misinterpretation of imaging criteria. This approach is in line with a recent publication from the European Association of Cardiovascular Imaging, stating that structural abnormalities in the absence of ECG changes should be interpreted with caution as this is unlikely to be caused by ARVC.[24] An example of the practical implementation of our results is depicted in *Figure 4*: in our cohort, ARVC could be ruled out in 138 (34%) patients using ECG and arrhythmia

criteria alone. An overview the simplification of the TFC is provided in the *Figure 5*.

Limitations

Our study population was drawn from two tertiary care centres, which may impact extrapolation to other settings. However, diagnosing ARVC is a complex process requiring a certain level of expertise which most often takes place in tertiary care centres (if not for initial diagnosis, then for second opinion). As this is an observational study, not all clinical tests were performed in all patients. For the analysis, we used appropriate statistical measures to correct for this. However, we cannot rule out the possibility that missing test results caused misclassification by the expert panel in certain cases, such as genetic analysis in borderline probands. To check for potential misclassification, the experts examined all available follow-up information. However, this would preferably require life-time follow-up, which was not available at the time of this study. Only six patients classified as 'at-risk for ARVC' developed ARVC during follow-up. Therefore, sub-analysis to evaluate the performance to identify early disease was not feasible. Since the expert review included all available test results, incorporation bias may have impacted our results. Nonetheless, as ARVC diagnosis is based on a large number of tests, and patients were scored by multiple experts independently, we expect this effect to be limited and equally distributed among tests. Finally, the results presented in this study depend on the assumption that the expert panel classification is the closest approximation of a gold standard, which is currently not available.

Conclusion

Using the largest cohort to date of patients consecutively evaluated for ARVC, our study shows that most individual TFC perform well, with the exception of SAECG and several family history criteria. Removing these criteria from the overall TFC score not only simplifies the TFC but also improves diagnostic accuracy. Furthermore, the relative weights of individual major and minor criteria as well as different categories may not be as equal as is currently assumed, suggesting the potential for possible improvement in future TFC iterations. Last, ECG and arrhythmia criteria alone can rule out ARVC with high sensitivity. This indicates that these criteria can be used as a first-line screening test, while limiting the use of more expensive imaging tests (echocardiography and CMR) among those unlikely to derive benefits from its results. Finally, this study underlies the need for an individual evaluation beyond the current criteria and to identify additional diagnostic tools for ARVC diagnosis.

Supplementary material

Supplementary material is available at *Europace* online.

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References

1. Basso C, Corrado D, Marcus FI, Nava A, Thiene G. Arrhythmogenic right ventricular cardiomyopathy. *Lancet* 2009;**373**:1289–300.
2. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A *et al.* Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Eur Heart J* 2015;**36**:3227–37.
3. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G *et al.* 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. *Br Heart J* 1994;**71**:215–8.
4. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA *et al.* Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J* 2010;**30**:806–14.
5. Borgquist R, Haugaa KH, Gilljam T, Bundgaard H, Hansen J, Eschen O *et al.* The diagnostic performance of imaging methods in ARVC using the 2010 Task Force Criteria. *Eur Heart J Cardiovasc Imaging* 2014;**15**:1219–25.
6. Platonov PG, Calkins H, Hauer RN, Corrado D, Svendsen JH, Wichter T *et al.* High interobserver variability in the assessment of epsilon waves: implications for diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Heart Rhythm* 2016;**13**:208–16.
7. Kamath GS, Zareba W, Delaney J, Koneru JN, McKenna W, Gear K *et al.* Value of the signal-averaged electrocardiogram in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Heart Rhythm* 2011;**8**:256–62.
8. Naaktgeboren CA, Bertens LC, van Smeden M, de Groot JA, Moons KG, Reitsma JB. Value of composite reference standards in diagnostic research. *BMJ* 2013;**347**:f5605.
9. Rutjes AW, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt P. Evaluation of diagnostic tests when there is no gold standard. A review of methods. *Health Technol Assess* 2007;**11**:iii, ix–51.
10. Reitsma JB, Rutjes AW, Khan KS, Coomarasamy A, Bossuyt PM. A review of solutions for diagnostic accuracy studies with an imperfect or missing reference standard. *J Clin Epidemiol* 2009;**62**:797–806.
11. Bertens LC, van Mourik Y, Rutten FH, Cramer MJ, Lammers J-WJ, Hoes AW *et al.* Staged decision making was an attractive alternative to a plenary approach in panel diagnosis as reference standard. *J Clin Epidemiol* 2015;**68**:418–25.
12. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007;**16**:219–42.
13. Rubin RB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley & Sons; 1987.
14. van Smeden M, de Groot JA, Moons KG, Collins GS, Altman DG, Eijkemans MJ *et al.* No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. *BMC Med Res Methodol* 2016;**16**:163.
15. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950;**3**:32–5.
16. Bomma C, Rutberg J, Tandri H, Nasir K, Roguin A, Tichnell C *et al.* Misdiagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Cardiovasc Electrophysiol* 2004;**15**:300–6.
17. Morin DP, Mauer AC, Gear K, Zareba W, Markowitz SM, Marcus FI *et al.* Usefulness of precordial T-wave inversion to distinguish arrhythmogenic right ventricular cardiomyopathy from idiopathic ventricular tachycardia arising from the right ventricular outflow tract. *Am J Cardiol* 2010;**105**:1821–4.
18. Avella A, d'Amati G, Pappalardo A, Re F, Silenzi PF, Laurenzi F *et al.* Diagnostic value of endomyocardial biopsy guided by electroanatomic voltage mapping in

arrhythmogenic right ventricular cardiomyopathy/dysplasia. *J Cardiovasc Electrophysiol* 2008;**19**:1127–34.
19. Peters S, Truemmel M, Koehler B. Prognostic value of QRS fragmentation in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *J Cardiovasc Med* 2012;**13**:295–8.
20. Cox M, van der Smagt JJ, Noorman M, Wiesfeld AC, Volders PGA, van Langen IM *et al.* Arrhythmogenic right ventricular dysplasia/cardiomyopathy diagnostic task force criteria: impact of new task force criteria. *Circ Arrhythm Electrophysiol* 2010;**3**:126–33.
21. Riele A, Te Bhonsale A, James CA, Rastegar N, Murray B, Burt JR *et al.* Incremental value of cardiac magnetic resonance imaging in arrhythmic risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol* 2013;**62**:1761–9.
22. Riele A, Te James CA, Rastegar N, Bhonsale A, Murray B, Tichnell C *et al.* Yield of serial evaluation in at-risk family members of patients with ARVD/C. *J Am Coll Cardiol* 2014;**64**:293–301.
23. Gupta R, Tichnell C, Murray B, Rizzo S, Riele Te A, Tandri H *et al.* Comparison of features of fatal versus nonfatal cardiac arrest in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Cardiol* 2017;**120**:111–7.
24. Haugaa KH, Basso C, Badano LP, Bucciarelli-Ducci C, Cardim N, Gaemperli O *et al.*; EACVI Scientific Documents Committee, EACVI Board members and external reviewers; EACVI Scientific Documents Committee, EACVI Board members and external reviewers. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy - an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2017;**18**:237–53.
25. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J *et al.*; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**:405–24.

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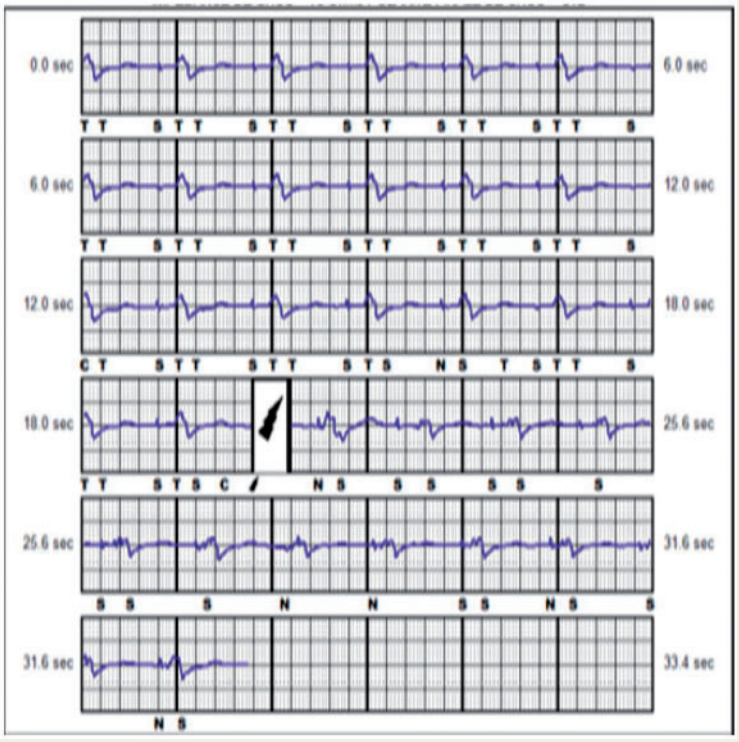
Inappropriate shock due to quadruple counting in a patient with subcutaneous implantable cardioverter-defibrillator and a dual-chamber pacemaker

Halim Marzak*, Olivier Morel, and Laurence Jesel

Pôle d'activité médico-chirurgical cardio-vasculaire, Nouvel Hôpital Civil, CHU de Strasbourg, 1, place de l'Hôpital, F-67091 Strasbourg, France

* Corresponding author. Tel: +33 (0)3 69 551467; fax: +33 (0)3 69 550970. *E-mail address*: halim.marzak@chru-strasbourg.fr



We report for the first time a case of inappropriate shock due to quadruple counting in the same episode in a 62-year-old patient implanted with a dual-chamber pacemaker and a subcutaneous implantable cardioverter-defibrillator (S-ICD), whereas appropriate electrocardiographic screening, S-ICD programming, and post-operative ergometric testing were carefully performed. He described one shock as unusual without palpitation nor syncope, while he was lying on the sofa. For this episode, ventricular electrogram analysis evidenced an intermittent oversensing of P and T waves associated with R-wave double counting due to paced wide QRS, leading to a false ventricular tachycardia (*Figure*). P-wave oversensing was due to unipolar atrial pacing and was corrected by programing an atrial bipolar stimulation mode. T-wave oversensing and R-wave double counting were suppressed by changing S-ICD primary sensing vector in secondary one. Comparing chest X-rays performed on admission and after S-ICD implantation, an inferior and posterior S-ICD displacement could be observed without any change in the lead position. After further investigation, he had presented 5 months ago a syncope due to fast ventricular tachycardia. He was successfully shocked while driving his tractor, which stopped in a ditch causing S-ICD displacement. After reprogramming the device, he did not experience any inappropriate shock until heart transplantation.

The full-length version of this report can be viewed at: https://www.escardio.org/Education/E-Learning/Clinical-cases/Electrophysiology.