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Screening relatives in arrhythmogenic right ventricular cardiomyopathy: yield of imaging and electrical investigations

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Aims Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited disease and presymptomatic screening of relatives is recommended. In 2010, the Task Force Criteria (TFC2010) introduced specific diagnostic imaging parameters. The aim of the study was to evaluate the diagnostic yield of family screening and the value of different diagnostic modalities.

Methods and results Family evaluation, including cardiac magnetic resonance (CMR), is routinely offered to ARVC relatives at our institution. We retrospectively registered baseline characteristics, symptomatology, and results of non-invasive examinations from 2010 to 2016 and assessed the findings according to TFC2010. A total of 286 relatives (150 females; age 12–76 years; 251 first-degree) were included. A total of 103 (36%) individuals reported cardiovascular symptoms. The non-invasive workup showed that 101 (35%) relatives had ≥1 positive parameter on signal-averaged electrocardiogram (ECG), 40 (14%) had abnormal findings on Holter monitoring, 36 (13%) fulfilled an ECG criterion, six (2%) fulfilled CMR criteria, and echocardiographic abnormalities was seen in one (0.3%) relative. In total, 21 (7% overall; 13% among gene-positive subgroup) relatives were diagnosed with ARVC and 78 (27% overall; 49% among gene-positive subgroup) with borderline ARVC based on the combined non-invasive evaluations. Family history and electrical investigations alone diagnosed 20 out of 21 (95%) ARVC cases and 73 out of 78 (94%) borderline cases.

Conclusion Consecutive evaluation of ARVC relatives diagnosed 7% with definite and 27% with borderline ARVC according to the TFC2010. Screening relatives for electrical abnormalities with 12 lead ECG, signal-averaged ECG, and Holter monitoring was more sensitive than imaging modalities.

Keywords ARVC • family screening • ECG • echocardiography • magnetic resonance imaging

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare familial disorder with a prevalence of approximately 1:5000. The disorder is predominantly inherited in an autosomal dominant manner and is pathologically characterized by myocyte loss and fibrofatty replacements in the myocardium. The clinical manifestations consist of a broad spectrum of symptoms from premature ventricular contractions (PVC) to heart failure, ventricular tachycardia and sudden cardiac death.[1–4]

ARVC is diagnosed as a syndrome based on published diagnostic criteria. The initial diagnostic Task Force Criteria were published in 1994[5] and updated in 2010 (TFC2010).[6] The TFC2010 encompasses a range of diagnostic modalities and include tissue characteristics, electrical abnormalities, genetic testing, family history, and structural/functional evaluation of ventricular sizes/function by cardiac magnetic

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resonance (CMR) and echocardiography. As part of the 2010 revision specific CMR and echocardiographic parameters were introduced to standardize quantification of right ventricular size and function. The TFC2010 imaging parameters include wall motion abnormalities (akinesia, dyskinesia, or dyssynchronous right ventricular contraction) and dilation of the right ventricle or decreased right ventricular ejection fraction (RVEF) (Supplementary data online, *Table S1*). The updated CMR parameters have shown a greater specificity for ARVC in probands[7] than the 1994 criteria. However, previous studies have shown that exercise can cause morphological changes in the right ventricle including dilatation. Thus, there is an overlap between diagnostically applied right ventricular volumes stated in TFC2010 and normal reference values.[8]

The general aim of the present study was to evaluate the overall diagnostic yield of routine clinical workup in ARVC relatives. Furthermore, we sought to quantify the prevalence of ARVC relatives meeting minor or major TFC2010 imaging criteria thereby evaluating the yield of imaging vs. electrical investigations to the diagnosis of ARVC in relatives.

Methods

Study population

We investigated a cohort of 286 relatives (134 families) to probands diagnosed with definite ARVC. Relatives to sudden cardiac death victims with autopsy findings consistent with ARVC were also included. All individuals were evaluated at a single tertiary centre, The Capital Regions Unit for Inherited Cardiac Diseases, Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Denmark between 1 January 2006 and 1 September 2016. The cohort was consecutive and included all relatives who had a full investigation for possible ARVC, including at least one CMR. The vast majority of relatives were first-degree relatives ($n = 251$), however, second-degree relatives ($n = 35$) were also offered evaluation if symptomatic and/or first-degree relatives were found to be affected or unavailable for screening. During the entire study period routine evaluation of ARVC relatives consisted of personal medical history, physical evaluation, routine biochemistry, 12 lead electrocardiogram (ECG), Holter monitoring, signal-averaged ECG, transthoracic echocardiography, and CMR. The investigations were repeated with 3- to 5-year intervals. Genetic testing was also routinely performed in probands and, if positive, cascade screening was offered to the relatives. All relatives, including those in whom a potentially disease-associated variant had been found in the proband, underwent initial clinical workup, but if investigations were normal and the relatives did not carry the probands variant, the relatives were reassured and follow-up was ceased. We excluded individuals who did not have a complete ARVC screening ($n = 12$), relatives who had a complete ARVC screening but the proband's ARVC diagnosis was later abandoned ($n = 2$), or had older CMR scans performed where the quality of the images did not allow complete evaluation according to TFC2010 ($n = 13$). All results were evaluated using the TFC2010 and patients were classified as either having definite ARVC (minimum of two major points, one major and two minor points, or four minor points), borderline ARVC (one major and one minor point or three minor points), or not fulfilling the TFC2010 for ARVC. The Danish Data Protecting Agency and Patient Safety Authority approved the study and authors had full access to the data.

Electrocardiography

Available 12-lead ECGs were evaluated in all patients and occurrence of depolarization abnormalities (epsilon waves or terminal activation duration ≥55 ms), repolarization abnormalities (T-wave inversions), and left/right bundle branch block were registered. TFC2010 was considered fulfilled if these pathologic findings were present on at least two ECGs.

Signal-averaged electrocardiography

Presence of late potentials and number of positive criteria were registered. If multiple signal-averaged ECGs had been performed in the same individuals the most abnormal was registered. If QRS width was >110 ms on the standard 12 lead ECG signal-averaged ECG was not performed.

Holter monitoring

All relatives had at least one 24-h Holter monitoring performed. If several monitorings had been performed in the same individual the most abnormal finding was registered, ranking (non-)sustained ventricular tachycardia over burden of PVC >500/24 h.

Echocardiography

Available transthoracic echocardiograms (TTE) were evaluated and we measured end-diastolic right ventricular outflow tract (RVOT) dimensions and occurrence of right ventricular functional abnormalities (akinesia, dyskinesia, or aneurysms). All echocardiographic evaluations were done by experienced operators, followed a standardized protocol, and operators were unaware of the overall diagnostic conclusion (affected, borderline, or unaffected). If several TTEs had been performed in the same individuals the newest TTE findings were analysed.

Cardiac magnetic resonance

By study design, all included relatives had at least one CMR performed. CMR scans were performed on a 1.5-Tesla scanner (Magnetom Avanto, Siemens, Germany) and all images were analysed independently using CVI42 (Circle Cardiovascular Imaging Inc., Canada). For quantification of the right ventricular volume and ejection fraction, we used 10–15 continuous slices throughout the right ventricle (steady-state free precession cine pictures with retrospective ECG-gating) in an axial view. We outlined the right ventricle endocardium in end-diastole and end-systole and calculated the right ventricle volume as a summation of measured volume in the individual slices. Afterwards we evaluated all slices searching for morphological changes in the right ventricle associated with ARVC (microaneurysms, thinning of the ventricular wall, hypertrabeculation, and wall motion abnormalities). Thinning of the right ventricular free wall was defined as <2 mm of wall thickness. Hypertrabeculation was assessed visually determining the degree and distribution of trabeculation in the right ventricle compared with normal controls. Fibrosis in the ventricles was investigated by presence of late enhancement using intravenous Gadolinium contrast.[9] Hingepoint fibrosis was not considered a pathologic finding. All CMR evaluations were done by experienced operators, followed a standardized protocol and operators were unaware of the overall diagnostic conclusion (affected, borderline, or unaffected). If several CMRs had been performed in the same individuals the newest CMR findings were analysed.

Results

Patient characteristics

The study population consisted of 286 relatives, mean age 38 (range 12–76) years, 150 (52.4%) were female, and 251 (87.8%) were

Table 1 Baseline characteristics

	No. of patients ($n = 286$)
Gender	
Female	150 (52%)
Male	136 (48%)
Relative status	
First degree	251 (88%)
Second degree	35 (12%)
Age (years at latest evaluation; range)	38 (12–76)
Height (cm; range)	175 (148–203)
Weight (kg; range)	75 (44–164)
Cardiovascular symptoms	
Palpitations	81 (28%)
Syncope of any cause	34 (12%)
NYHA ≥ 2	10 (3%)
CCS ≥ 1	25 (9%)
Genetic testing[a]	
No variant	34 (47%)
Presumed disease-associated variant identified	39 (53%)

Data are presented as mean values (range) or numbers (%).
[a]Genetic testing was performed in a total of 73 relatives from 54 families.
CCS, Canadian Cardiovascular Society grading of angina pectoris; NYHA, New York Heart Association functional classification.

first-degree relatives, and 35 (12.2%) second degree. All relatives were of Caucasian descent. Cardiac symptoms were present in 103 (36%), the most common symptom being palpitations. By study design, all subjects scored either a minor or major point for positive family history using the TFC2010. Patient characteristics are summarized in *Table 1*.

Genetics

Out of the 134 probands a possible, probable, or confirmed disease-associated genetic variant was found in 54 (40%). In these families with a positive genetic result cascade testing was performed in 73 relatives with a positive genetic finding in 39 (53% of relatives tested; 14% of entire cohort). The most commonly involved genes were *PKP2*, *DSG2*, *DSP*, and *JUP*. Thirty-four gene-negative relatives from gene-positive probands were also evaluated and six borderline cases were found in this subgroup (no definite ARVC cases). Genetic variants (and their classification) identified in relatives are listed in Supplementary data online, *Table S2*.

Electrical abnormalities

Analyses of 12 lead ECGs showed that six relatives (2.1%) had a major criterion in the repolarization category by having T-wave inversion in precordial leads V1–V3 without the presence of right bundle branch block. Furthermore, 18 (6.3%) relatives had a minor criterion by having T-wave inversion in V1–V3 under the presence of a RBBB, and four (1.4%) had T-wave inversion in V1 and V2 without the presence of RBBB. In the depolarization category, a total of five (2%) relatives had an epsilon wave in at least one ECG, but only two (0.7%) had a consistent epsilon wave in at least 2 ECGs thereby fulfilling a TFC2010 major criterion. A total of six (2.1%) relatives scored a minor point because of terminal action duration ≥55 ms. Analysing signal-averaged ECGs, a total of 101 (35.3%) relatives had a minor criterion by having at least one positive parameter thereby being the most commonly found abnormality in the investigated subjects. Analyses of Holter monitorings showed that two (0.7%) individuals fulfilled a major point in this category by having non-sustained VT with left bundle branch block (LBBB) morphology and a superior axis. Furthermore, five (1.7%) individuals had non-sustained VT with LBBB morphology but with inferior or undeterminable axis, and 33 (11.5%) subjects had >500 PVCs/24 h thereby fulfilling a minor criterion. The presence of a PVC burden >500/24 h was the second most commonly found abnormality in the investigated population. Results are summarized in *Table 2*.

Echocardiography

The mean RVOT/BSA dimension for the newest available TTE was 16.4 (range 8.5–27) mm/m^2. In total, 36 (12.6% of cohort; four gene-positive = 10.3% of gene-positive) relatives had a dilated RVOT/BSA, but only one (not genotyped) individual had accompanying wall motion abnormalities of the right ventricle thereby fulfilling a TFC2010 minor criterion. Representative images are presented in *Figure 1*.

Cardiac magnetic resonance

The mean end-diastolic volume of the right ventricle was 166 (range 68–334) mL and the mean BSA-indexed end-diastolic right ventricular volume was 87 (range 31–145) mL/mm^2. In total, 66 (23.1%; five gene-positive = 12.8% of gene-positive) relatives had a dilated right ventricle according to the TFC2010. The mean RVEF was 58% (range 34–79). Overall six (no gene-positive) relatives had a decreased RVEF under 45% (four between 40% and 45%; two under 40%). Other CMR findings included six relatives (no gene-positive) with wall motion abnormalities (hypokinesia of the myocardium and/or microaneurysms). For other pathologic findings possibly associated with ARVC, 10 relatives (3.5%; four gene-positive = 10.3% of gene-positive) had hypertrabeculation and/or thinning of the right ventricular wall. Late gadolinium enhancement (performed in 184 relatives) was found in one or more segments in 15 (8.2% of cohort tested; one gene-positive = 2.6% of gene-positive) relatives. Representative images are presented in *Figure 1*.

A total of six (2.1%; no gene-positive) relatives fulfilled the diagnostic criteria for CMR, i.e. wall motion abnormalities as well as a dilated right ventricle were present. CMR data are summarized in *Table 3*.

Combined diagnostic yield in ARVC relatives

Of the 286 included relatives in our study, 21 (7.3% overall; five gene-positive = 12.8% of gene-positive vs. 7.5% of gene-unknown relatives) were diagnosed with ARVC according to TFC2010 based on at least two major criteria ($n = 10$), one major and two minor criteria ($n = 11$), or four minor criteria ($n = 0$). The affected relatives were diagnosed based on their family disposition and criteria from the following categories: Arrhythmia and depolarization abnormalities (12 patients), arrhythmia and repolarization abnormalities (four patients), repolarization and depolarization abnormalities (three patients), depolarization abnormalities (one patient), and arrhythmia and

Table 2 Results of non-invasive evaluation (excluding CMR) in 286 ARVC relatives

Structural abnormalities	Total (*N* = 286), *n* (%)	TFC+ (*N* = 21), *n* (%)	TFC– (*N* = 265), *n* (%)	Gene+[a] (*N* = 39), *n* (%)	Gene–[a] (*N* = 34), *n* (%)
Echocardiogram: dilated RVOT/BSA (PSAX)	36 (13)[b]	1 (5)	35 (13)	4 (10)	3 (9)
Major: PSAX RVOT/BSA ≥ 21 mm + WMA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Minor: PSAX RVOT/BSA ≥ 19 mm + WMA	1 (<1)	1 (5)	0 (0)	0 (0)	0 (0)
Repolarization abnormalities					
Major	6 (2)	2 (10)	4 (2)	1 (3)	0 (0)
Inverted T waves in leads V1–V3 or beyond (no RBBB)	6 (2)	2 (10)	4 (2)	1 (3)	0 (0)
Minor	22 (8)	6 (29)	16 (6)	3 (8)	2 (6)
Inverted T waves in leads V1 and V2 (no RBBB)	4 (1)	4 (19)	0 (0)	0 (0)	2 (6)
Inverted T waves in leads V1–V3 (RBBB)	18 (6)	2 (10)	16 (6)	3 (8)	0 (0)
Arrhythmias					
Major	2 (<1)	1 (5)	1 (<1)	0 (0)	1 (3)
Non-sustained VT (LBBB with superior axis)	2 (<1)	1 (5)	1 (<1)	0 (0)	1 (3)
Minor	38 (13)	12 (57)	26 (10)	11 (28)	4 (12)
≥500 PVC/24 h	33 (12)	9 (43)	24 (9)	8 (21)	4 (12)
Non-sustained VT (LBBB with inferior or indefinite axis)	5 (2)	3 (14)	2 (<1)	3 (8)	0 (0)
Depolarization abnormalities					
Major	2 (<1)	1 (5)	1 (<1)	0 (0)	0 (0)
Epsilon wave	5 (2)[c]	1 (5)[c]	4 (2)[c]	0 (0)	0 (0)
Minor	107 (37)	15 (71)	92 (35)	12 (31)	7 (21)
Late potentials by signal-averaged ECG in ≥1 parameter	101 (35)	14 (67)	87 (33)	12 (31)	7 (21)
Terminal action duration ≥55 ms	6 (2)	1 (5)	5 (2)	0 (0)	0 (0)

BSA, body surface area; CMR, cardiac magnetic resonance; gene +/–, mutation testing positive/negative; LBBB, left bundle branch block; PSAX, parasternal short-axis; PVC, premature ventricular contraction; RBBB, right bundle branch block; RVOT, right ventricular outflow tract; TFC+/–, Task Force Criteria fulfilled/not fulfilled; TTE, transthoracic echocardiography; VT, ventricular tachycardia; WMA, wall motion abnormalities.

[a]In total, 73 relatives genetically tested. Percentages shown as observed number of gene-positive (Gene+) or gene-negative (Gene–) relatives with fulfilled TFC criteria divided with the total number of gene-positive or gene-negative relatives, respectively. No significant difference was found between the two groups for any diagnostic modality (all *P*-value >0.05).

[b]To fulfil the Task Force 2010 diagnostic criteria the patient must have regional abnormalities in the right ventricular wall (i.e. akinesia, dyskinesia, or aneurysm) as well as dilation of RVOT.

[c]Five relatives had an epsilon wave in an ECG, but only two (0.7%) had an epsilon wave in >1 ECG.

structural abnormalities (TTE, one patient) (*Figure 2A*). Furthermore, we found that 78 (27% overall; 19 gene-positive = 48.7% of gene-positive vs. 24.9% of gene-unknown relatives) relatives had borderline ARVC based on either one major and one minor criterion or three minor criteria. The positive findings were distributed as seen in *Figure 2B*, with depolarization abnormalities being the most common finding followed by arrhythmia and repolarization abnormalities.

Grouping of investigations into electrical (12 lead ECG, signal-averaged ECG, Holter monitoring) and imaging (echocardiography and CMR) showed that based on family history and electrical investigations alone, 20 relatives (7.0%) would have been have been diagnosed with ARVC and 73 relatives (26%) with borderline ARVC. Based on family history and imaging alone no relatives (0%) would have been diagnosed with ARVC and six (2.1%) with borderline ARVC. In total, family history and electrical investigations alone diagnosed 20 out of 21 (95%) ARVC cases and 73 out of 78 (94%) borderline cases.

Analysis of the gene-positive subgroup (39 relatives), showed that five (12.8%) relatives fulfilled ARVC criteria and 19 (48.7%) borderline ARVC (Supplementary data online, *Table S3*). Electrical investigations alone would have diagnosed all five (100%) with ARVC and all 19 (100%) with borderline ARVC, whereas imaging would have not have diagnosed any (0%) relatives with definite or borderline ARVC. No significant difference was found between the yield in the gene-positive and gene-negative group for any diagnostic modality (all $P > 0.05$).

Discussion

Comprehensive workup in this consecutive cohort of 286 ARVC relatives identified 21 (7.3%) of the overall population of ARVC relatives with definite ARVC according to the TFC2010. In the subgroup of gene-positive first-degree relatives, 14% was diagnosed with ARVC. The affected relatives were primarily diagnosed based on electrical abnormalities. Imaging provided low diagnostic yields. Only six (2.1%) relatives fulfilled a CMR diagnostic TFC2010 criterion and one (<1%) relative fulfilled an echocardiographic criterion.

The cohort primarily consisted of first-degree, young individuals with an equal gender distribution. Cardiovascular symptoms were

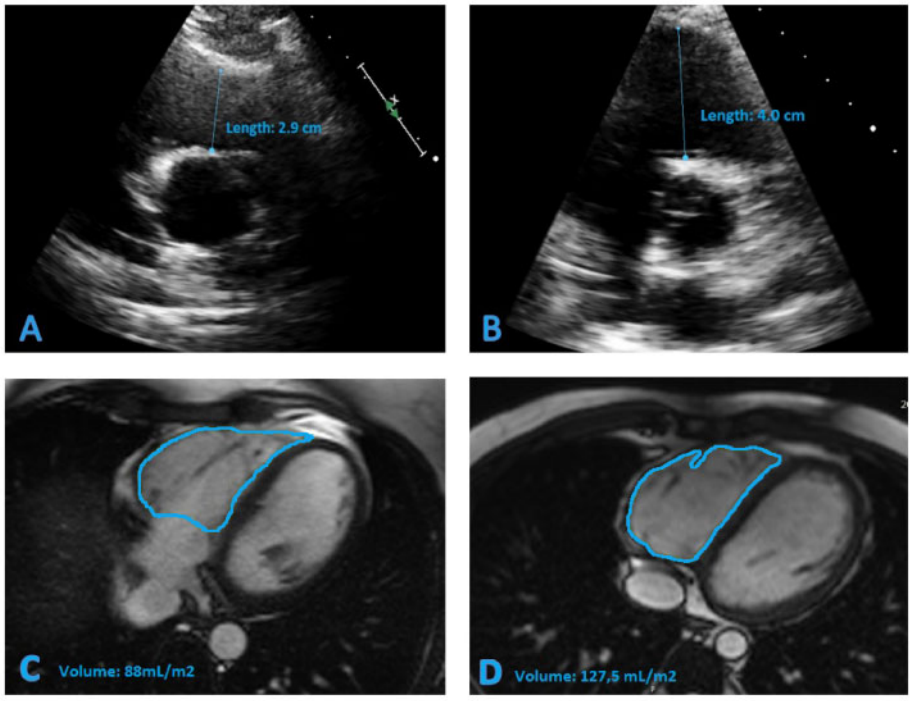

Figure 1 Evaluation of the right ventricle with echocardiography and CMR imaging. (*A*, *B*) Representative end-diastolic echocardiographic images with a normal (A) and dilated (B) RVOT. (*C*, *D*) CMR-based measurement of the right ventricular volume in end-diastole (RVEDV) in a relative with normal findings (C) and a dilated right ventricle (D).

Table 3 Results of CMR imaging in 286 ARVC relatives

	Total (*N* = 286)	TFC+ (*N* = 21)	TFC– (*N* = 265)	Gene+[a] (*N* = 39)	Gene–[a] (*N* = 34)
Right ventricular end-diastolic volume					
RVEDV/BSA (range) (mL/m^2)	87 (31–145)	93 (67–139)	86 (31–145)	85 (31–118)	83 (47–125)
Patients with dilated RVEDV/BSA	66 (23%)	5 (24%)	61 (23%)	8 (21%)	8 (24%)
Right ventricular function					
Right ventricular ejection fraction (%, range)	58 (34–79)	55 (34–65)	58 (39–79)	59 (48–73)	58 (47–76)
Patients with a decreased RVEF <45%	6 (2%)	2 (10%)	4 (2%)	0 (0)	0 (0)
Wall motion abnormalities (aneurysms, hypokinesia, or akinesia)	6 (2%)	0 (0)	6 (2%)	1 (3%)	0 (0)
Other CMR findings not part of the 2010TFC	22 (8%)[b]	1 (5%)	21 (8%)[b]	5 (13%)	1 (3%)
Late gadolinium enhancement[c]	15 (8%)	1 (5%)	14 (5%)	1 (3%)	1 (3%)
Hypertrabeculation and/or thinning of the right ventricle	10 (4%)	0	10 (4%)	4 (10%)	0 (0)
Patients fulfilling CMR 2010TFC	6 (2%)	1 (5%)	5 (2%)	0 (0)	0 (0)
Major	1 (<1%)	0 (0)	1 (<1%)	0 (0)	0 (0)
Minor	5 (2%)	1 (5%)	4 (2%)	0 (0)	0 (0)

2010TFC, Task Force Criteria published in 2010; ARVC, arrhythmogenic right ventricular cardiomyopathy; BSA, body surface area; CMR, cardiac magnetic resonance; Gene +/–, mutation testing positive/negative; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; TFC+/–, Task Force Criteria fulfilled/not fulfilled.

[a]In total, 73 relatives genetically tested. Percentages shown as observed number of gene-positive (Gene+) or gene-negative (Gene–) relatives with fulfilled TFC criteria divided with the total number of gene-positive or gene-negative relatives, respectively. No significant difference was found between the two groups for any diagnostic modality (all *P*-value >0.05).

[b]Three relatives had both hypertrabeculation and/or thinning of the right ventricle as well as late gadolinium enhancement.

[c]Late gadolinium enhancement was performed in 184.

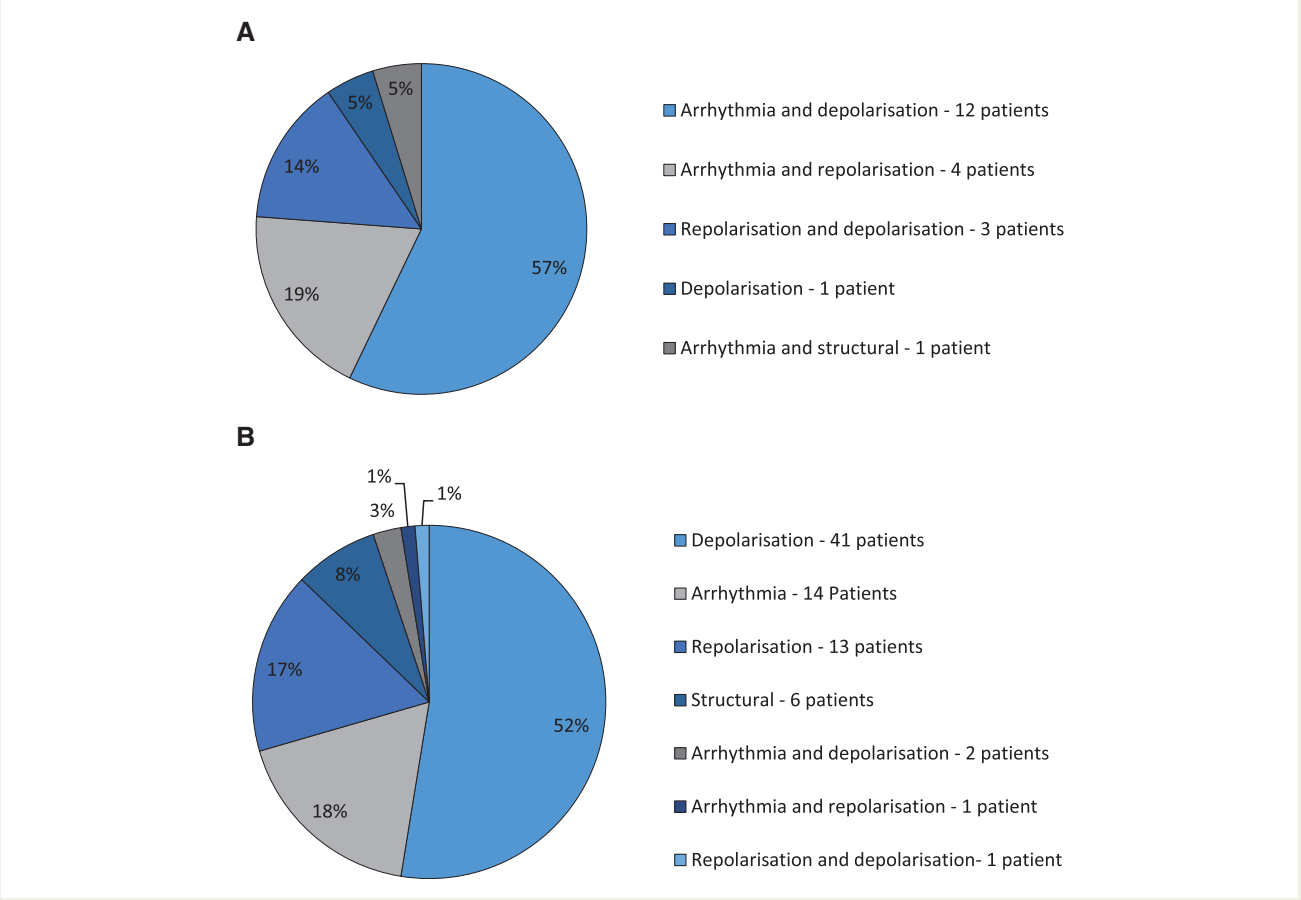

Figure 2 Distribution of the Task Force criteria in relatives screened for ARVC. All included relatives fulfilled either a minor or major criteria for relative status. (*A*) Distribution of fulfilled criteria in relatives who were diagnosed with ARVC. (*B*) Distribution in relatives who had borderline ARVC (one major and one minor point or three minor points, including relative status).

common (36%) with palpitations being the most reported symptom (28%) followed by syncope (12%). Cardiac symptoms are very common in the Danish general population among all age groups[10] and participation in a screening programme for inherited heart disease likely contributes to an increased awareness of symptoms and reporting unspecific symptoms as possible cardiac. An earlier study has found that palpitations and syncope are the most two common symptoms in ARVC probands[11] which was supported by our findings. Another previous study reported a prevalence of symptoms in 39% of ARVC relatives,[12] but the study had a much higher representation of gene-positive relatives, and therefore as expected a much higher diagnostic yield, suggesting a population at a higher risk.

Routine screening for electrical abnormalities included ECG, signal-averaged ECG, and Holter monitoring. Late potentials on signal-averaged ECG, defined as ≥1 positive parameter, was the most common positive findings (35%) consistent with previous studies.[12] The presence of late potentials is not a specific parameter of cardiomyopathy and may be positive in 10% of normal controls and is influenced by numerous cardiac and non-cardiac factors[13,14] but has been shown to have diagnostic value in ARVC.[15,16] The second most common positive finding was a high burden of PVC on Holter followed by T-wave inversions. A previous study of ARVC relatives has found a similar rate of an abnormal PVC burden (16% vs. 13% in our study), but reported a higher prevalence of T-wave inversions (34% vs. 10% in our study).[12] Epsilon waves were very uncommon and have been reported as a finding with low reproducibility.[17] Transthoracic echocardiography found a dilated RVOT in 13%, but associated wall motion abnormalities were exceedingly rare. This finding may be interpreted as either dilation precedes wall motion abnormalities in early ARVC, or, that the suggested reference values for right ventricular dimensions have a significant overlap with findings in the normal population. Indeed, it has been shown that intense physical exercise can cause right ventricular dilatation but usually not motion abnormalities.[18]

Routine use of CMR in screening of ARVC resulted in a low diagnostic yield in the initial screening of ARVC relatives. The low diagnostic yield of CMR was consistent with a smaller study of relatives from North America[19] and a Chinese study showing that introduction of TFC2010 CMR criteria reduced the number of ARVC patients meeting any form of CMR criteria from 23% to 3%.[7] Our study confirmed that right ventricular dilatation is a common finding (27%) in our younger population but accompanying wall motion abnormalities were very rare. We found an even lower number of patients meeting any CMR criteria, thus supporting that electrical abnormalities

precede structural abnormalities in ARVC. It should also be noted that TFC2010 do not take age and physical activity into consideration, which may be particularly important in relatives undergoing routine screening as young adults. Reference values for normal right ventricular volume overlap with ARVC diagnostic critieria.[8] In most of the relatives with a dilated RVEDV, the observed dilation was only a few millilitres suggesting that a discrete dilatation should be considered a non-pathologic finding in young adults without other signs of disease. Late gadolinium enhancement was found in 5% of relatives, whereas it has been reported in 36% of ARVC probands.[20] Late gadolinium enhancement correlates with electrophysiological abnormalities[21] and is a risk factor for sudden cardiac death in other cardiomyopathies.[22] Other non-diagnostic CMR findings included hypertrabeculation and thinning of the right ventricular free wall; findings that should be interpreted with caution as it may lead to over-diagnosis of ARVC.[23]

Application of standardized consecutive evaluation of ARVC relatives resulted in a diagnostic yield of 7%. Borderline findings were identified in additional 27%. Previous studies reported a diagnostic yield 10–37% in first-degree relatives.[12,24] In our study, screening for electrical abnormalities was much more sensitive than imaging, which had low incremental diagnostic value in accordance with previous smaller studies.[12,25] Our overall diagnostic yield was relatively modest presuming an autosomal dominant mode of inheritance. Although reduced and age-/gender-related penetrance,[26] and variable expressivity are important explanatory factors, emerging evidence suggest that a desmosomal genetic variant may not be sufficient to cause a full-blown ARVC-phenotype and that environmental factors, in particular rigorous exercise, are crucial modifiers.[27,28] Our cohort consists of consecutively referred relatives and it is important to underline that subgroups exist where the risk of disease is likely higher, e.g. if focusing on gene-positive first-degree relatives, families with proven familial disease (≥2 affected members), or patients with specific genotypes (e.g. *TMEM43* or *FLNC*). Other possible explanations for the differences in diagnostic yields between our and previous studies include relatively low age of relatives at evaluation in our study, differences in study design (some studies included only gene-positive relatives), differences in referral patterns (only the most severe cases with prominent family history referred), and different modes of inheritance studied.

The present study has the limitation of being retrospective in design, but did include a large number of consecutive relatives that underwent a very standardized programme. A proportion of the probands had not undergone genetic testing and the resulting population of genotype-unknown relatives may not be directly comparable with previous studies that primarily consisted of gene-positive relatives. Furthermore, the pathogenicity of many ARVC-associated variants cannot be confirmed definitively. Moreover, although the proband's ARVC diagnosis was verified before inclusion of their relatives in the current study, we do not routinely perform myocardial biopsies. Due to this lack of histological confirmation in the majority of probands, we cannot rule out a minor proportion had ARVC phenocopies, e.g. cardiac sarcoidosis or myocarditis. Lastly, exercise data—a potential important modifier of ARVC—were not available.

In conclusion, we find a relatively low diagnostic yield of 7% when screening ARVC relatives. We confirm that screening for electrical abnormalities with standard 12 lead ECG, signal-averaged ECG, and Holter monitoring is more sensitive than imaging modalities. Both echocardiography and CMR identified a large proportion of relatives with a mildly dilated right ventricle but without accompanying wall motion abnormalities or signs of electrical abnormalities suggesting non-disease-associated physiological adaptation. Echocardiography and CMR are central diagnostic modalities within the field of cardiomyopathies and we do not advocate diagnosing ARVC without use of imaging modalities, but our data suggest that initial evaluation of asymptomatic ARVC relatives may be performed without routine CMR in individuals with no signs of electrical abnormalities.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflict of interest: none declared.

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