High penetrance and similar disease progression in probands and in family members with arrhythmogenic cardiomyopathy

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Aims
We aimed to assess structural progression in arrhythmogenic cardiomyopathy (AC) patients and mutation-positive family members and its impact on arrhythmic outcome in a longitudinal cohort study.

Methods and results
Structural progression was defined as the development of new Task Force imaging criteria from inclusion to follow-up and progression rates as annual changes in imaging parameters. We included 144 AC patients and family members (48% female, 47% probands, 40 ± 16 years old). At genetic diagnosis and inclusion, 58% of family members had penetrant AC disease. During 7.0 [inter-quartile range (IQR) 4.5–9.4] years of follow-up, 47% of family members without AC at inclusion developed AC criteria, resulting in a yearly new AC penetrance of 8%. Probands and family members had a similar progression rate of right ventricular outflow tract diameter (0.5 mm/year vs. 0.6 mm/year, \(P = 0.28\)) by mixed model analysis of 598 echocardiographic examinations. Right ventricular fractional area change progression rate was even higher in family members (-0.6%/year vs. -0.8%/year, \(P < 0.01\)). Among 86 patients without overt structural disease or arrhythmic history at inclusion, a first severe ventricular arrhythmic event occurred in 8 (9%), of which 7 (88%) had concomitant structural progression. Structural progression was associated with higher incidence of severe ventricular arrhythmic events adjusted for age, sex, and proband status (HR 21.24, 95% CI 2.47–182.81, \(P < 0.01\)).

Conclusion
More than half of family members had AC criteria at genetic diagnosis and yearly AC penetrance was 8%. Structural progression was similar in probands and family members and was associated with higher incidence of severe ventricular arrhythmic events.

Keywords
Arrhythmogenic cardiomyopathy • Structural progression • Arrhythmic risk • Penetrance

Introduction
Arrhythmogenic cardiomyopathy (AC) is an inheritable and progressive heart muscle disease caused by dysfunctional cardiac desmosomes.1 The natural history of AC is characterized by life-threatening ventricular arrhythmias (VA) and risk of sudden cardiac death (SCD) in young adults2 in addition to morphological abnormalities and eventually heart failure.3 Arrhythmogenic cardiomyopathy is commonly concealed until adolescence and has incomplete penetrance and variable progression,4 which makes the disease outcomes
difficult to predict. Genetic testing has provided the opportunity to identify family members at risk of developing AC. These individuals need follow-up to assess their risk of SCD. The timing of prophylactic implantable cardioverter-defibrillator (ICD) implantation is crucial and is often guided by the occurrence of VA and the development of structural abnormalities.

Probands commonly present with advanced structural disease, while family members may have no or early disease at first encounter. Proband status is also associated with worse outcome of AC disease. However, structural disease progression rate in family members compared with probands is unknown. We aimed to assess penetrance of family members at genetic diagnosis and during follow-up and compare disease progression in AC probands and family members in a longitudinal cohort study.

Methods

Study population
We included patients diagnosed with AC at Oslo University Hospital, Rikshospitalet, Norway, after 1997 with at least two complete clinical evaluations of which 94 were previously reported. Inclusion was defined at the time of first echocardiography on compatible hardware (GE Vivid 7, E9 or E95, EchoPac 201, GE Vingmed, Horten, Norway). Last clinical follow-up was the last clinical visit including an echocardiographic examination before death, cardiac transplantation or January 2018. We analysed all echocardiograms between inclusion and last follow-up. Demographic data, clinical characteristics at inclusion, proband status, and family history were recorded. Patients were interviewed about their exercise habits before AC diagnosis as previously described. All patients were advised to refrain from vigorous exercise and to reduce any kind of exercise and they affirmed to have followed medical advice at regular follow-up visits.

We defined a proband as the first person in a family to exhibit clinical symptoms or signs that triggered an evaluation of AC. Genetic testing was performed in all probands fulfilling current Task Force Criteria (TFC). Family members of probands with pathogenic mutations underwent cascade genetic screening and were included if mutation-positive. Patients with other cardiopulmonary comorbidities were excluded. We defined severe ventricular arrhythmic events in previously arrhythmia free patients as aborted cardiac arrest (ACA), sustained ventricular tachycardia (SustVT) (ventricular beats >100 b.p.m. for >30 s) documented on 12-lead electrocardiographic (ECC) or Holter, ventricular tachycardia (VT) or ventricular fibrillation (VF) terminated by antitachycardia pacing (ATP) or shock from a primary preventive ICD.

Written informed consent was given by all patients. The study complied with the declaration of Helsinki and was approved by the Regional Medical Ethics Committee of South-Eastern Norway.

Electrical progression
Electrocardiogram, signal-averaged ECG, and Holter recordings at the time of inclusion and last clinical follow-up were analysed according to TFC. Ventricular tachycardia of inconclusive configuration was included in the minor arrhythmia criteria category. Electrical progression was defined as gaining a minor or major repolarization or depolarization criterion or fulfilling the criterion of >500 premature ventricular complexes (PVC)/24 h during follow-up.

Structural and functional progression
All complete echocardiographic examinations in sinus rhythm between inclusion and last clinical follow-up were analysed. We measured right ventricular (RV) outflow tract (RVOT) diameter in parasternal short-axis view, RV basal diameter (RVD) and RV fractional area change (RVFAC). All echocardiographic views, including the subcostal view, were used to detect RV akinesia, dyskinesia, or aneurysms. We assessed left ventricular (LV) function by LV ejection fraction (LVEF) and LV global longitudinal strain (LVGLS), defined as the average peak systolic strain in 16 LV segments. LV mechanical dispersion (MD) was defined as the standard deviation of time from Q/R on surface ECG to peak negative strain in 16 LV segments.

Cardiac magnetic resonance (CMR) imaging was performed in 94 patients at inclusion and in 15 patients at last follow-up and evaluated according to TFC. We defined structural disease progression as the development of new TFC imaging diagnostic criteria from inclusion to follow-up. The annual rate of progression in imaging parameters was calculated by linear mixed model analysis.

All measurements were performed blinded to clinical outcome. Intra- and inter-observer variability was assessed by reanalysing 10 random echocardiographic studies (Supplementary material online, Table S1). Myocardial biopsy was performed on clinical indication according to TFC.

Statistics
Continuous data were presented as mean with standard deviation or median with inter-quartile range (IQR) and categorical data as numbers (percentages). Continuous variables were compared using the independent Student’s t-test for parametric or Mann–Whitney U test for non-parametric variables and categorical data using χ² or Fisher’s exact tests. Non-parametric repeated measurements were compared by the McNemar test.

Cox regression was performed to assess markers of first severe ventricular arrhythmic event during follow-up. Intra- and inter-observer variability was expressed by intraclass correlation coefficient (IBM SPSS v.23).

Key parameters from all echocardiographic assessments during the study period were entered into a linear mixed model with random intercept and exchangeable covariance structure. Structural and functional deterioration in probands vs. family members was assessed by an interaction term between proband status and time since first assessment.

Separate analyses were performed excluding mutation-negative probands and we performed sub-analyses in plakophilin-2, desmoglein-2/desmoplakin (DSG2/DSP) patients and in patients with and without structural disease at inclusion (Stata SE 15.2).

Results

Clinical characteristics
We included 144 AC patients or mutation-positive family members (40 ± 16 years old, 48% female) of which 68 were probands and 76 were family members (53% first, 29% second, 17% third degree family members). Median follow-up was 7.0 years (IQR: 4.5–9.4), slightly longer for probands than for family members (Table 1). The majority of probands (66%) had severe VA at time of inclusion, whereas no family member had experienced previous severe arrhythmic events (P < 0.001) (Table 1). Probands were exposed to higher previous exercise intensity than family members (P < 0.001) (Table 1).

Disease penetrance in family members
Among the 76 family members, 31 (41%) had definite AC diagnosis and 13 (17%) had borderline AC diagnosis at first evaluation, giving a
58% AC disease penetrance in family members identified by family screening (Figure 1).

The remaining 32 (42%) family members had neither imaging nor electrical criteria at inclusion. Of the 32 family members with no AC disease at inclusion, 15 (47%) had disease penetrance (any addition of minor or major structural criteria from TFC) during 5.7 (IQR: 4.1–8.2) years of follow-up, whereas 17 (53%) remained free of any structural or electrical criteria (Figure 1), indicating 8% (47% over 6 years) yearly AC penetrance in family members. Isolated electrical penetrance occurred in 9 family members, 3 had isolated structural penetrance, and 3 had both electrical and structural penetrance. No difference in penetrance was observed between 1st, 2nd- or 3rd-degree family members at inclusion (55%, 60%, and 62%, \( P = 0.95 \)) nor at last follow-up (73%, 86%, and 77%, \( P = 0.63 \)).

### Structural and functional progression among probands and family members

At inclusion, probands had more severe disease compared with family members, with more frequent major imaging criteria (Table 2) and worse cardiac function (Table 3), as expected. The prevalence of major imaging criteria increased and more patients fulfilled definite AC diagnosis at follow-up (Table 2, Supplementary material online, Table S2). Among 114 patients without major imaging criteria at inclusion, 49 (43%) patients had structural progression during follow-up.

Among the 68 probands, 27 (40%) had overt structural phenotype with major imaging TFC at inclusion. During 8.2 (IQR: 5.8–11.2) years follow-up, 24 probands (35%) developed structural progression, whereas 17 probands (25%) did not develop additional criteria and were defined as structural non-progressors. Right ventricular dimensions increased and RV function and LV function by LVGLS worsened during follow-up (Table 3).

Among the 76 family members, 3 (4%) had major imaging criteria at inclusion. During 5.4 (IQR: 4.1–8.7) years of follow-up, structural progression occurred in 25 (33%), and 48 (63%) were structural non-progressors. Similar to probands, both RV and LV parameters deteriorated with a slow yearly change during follow-up (Table 3).

Exercise intensity was associated with structural progression in the total material also when adjusted for proband status (adjusted OR 1.3, 95% CI 1.0–1.7, \( P = 0.03 \)) and in separate analyses of family members (OR 1.6, 95% CI 1.1–2.5, \( P = 0.02 \)). Higher LV MD predicted structural progression only in family members (OR 1.6, 95% CI 1.1–2.4, \( P = 0.02, \) per 10 ms), whereas ECG T-waves inversions were not predictive (\( P = 0.14 \)).

### Comparison of structural and functional progression in probands and family members

Right ventricular function by RVFAC deteriorated by absolute 0.7% (95% CI 0.66–0.80) yearly, and RVOT diameter increased by 0.5 mm (95% CI 0.47–0.59) yearly, whereas LV function deteriorated by absolute 0.1% (95% CI 0.06–0.13) yearly worsening of LVGLS.

In linear mixed model analysis of all 598 echocardiographic assessments in 144 patients (median 4, IQR 3–5), probands and mutation-positive family members had similar disease progression for RV and LV parameters, except for RVFAC that decreased more rapidly in family members (Table 3 and Figure 2). This was also evident after adjustment for possible confounders at inclusion (data not shown).

We observed no major differences in structural progression between patients with and without structural disease at inclusion (Supplementary material online, Table S3), nor when excluding mutation-negative probands (Supplementary material online, Table S4). There was an insignificant tendency towards a higher rate of LVEF decrease in DSG2/DSP compared with PKP2 mutation-positive patients (\( P = 0.06 \)), whereas PKP2 mutation-positive patients had higher rate of RVFAC decrease (\( P = 0.04 \)) (Supplementary material online, Table S5).

### Electrical progression

Probands had more electric criteria at inclusion compared with family members, as expected (Table 2). The prevalence of depolarization criteria increased during follow-up (Table 2). Incidence of prolonged terminal activation duration increased during follow-up, and
Among the 99 (69%) patients without severe VA at inclusion, 14 (14%) experienced severe VA (1 ACA, 5 SusVT, 4 VT + 1 VF ICD-shock, 3 ICD-ATP) during 6.2 (IQR: 4.2–9.2) years of follow-up. First severe VA was more common in probands (10, 44%), but occurred also in family members (4, 5%).

Among 61 patients with ICD at follow-up (Table 2), severe VA was detected in 17/61 (88% probands) (5 ATP, 6 VT + 6 VF shock), of whom 15 (88%) had structural disease.

## Association between ventricular arrhythmias and structural progression

Among 86 patients without overt structural disease or arrhythmic history at inclusion, a first severe ventricular arrhythmic event occurred in 8 (9%) of which 7 (88%) had concomitant structural progression. Structural progression was associated with arrhythmic events independent of age, sex and proband status (Table 4). All four family members who had their first severe arrhythmic event during follow-up had also structural progression (Figure 3) and progressed from an electrical phase and acquired new structural abnormalities criteria during follow-up. No arrhythmic death occurred during follow-up.

## Discussion

This study showed that (i) >50% of family members diagnosed by family screening had signs of AC disease at first evaluation. Another 50% of those without disease at first evaluation developed electrical or structural findings during 6 years of follow-up highlighting the need of family screening and close family follow-up; (ii) structural disease progressed at similar rate in probands and in family members; (iii) structural progression was independently associated with increased risk of first severe arrhythmic event during follow-up, emphasizing the increased arrhythmic risk when structural changes are detected.

## Disease penetrance in family members

More than half (58%) of family members diagnosed by family screening had signs of AC disease at first evaluation, indicating a high disease penetrance at first evaluation, in line with previous reports. These results highlight the importance of genetic cascade screening in family members to identify individuals at increased risk of VA. Most importantly, we found a 5% 5 year risk of severe VA occurrence in family members, highlighting that continuous follow-up and evaluation of arrhythmic risk is crucial in AC family members. In family members without signs of AC disease at first evaluation, 50% developed structural or electrical abnormalities during follow-up, with an estimated 41% 5 year risk or 8% yearly risk of developing signs of AC disease. Previous reports have indicated disease progression in 25–30% of family members over 4 years of follow-up. Our results support previous reports showing an even higher disease progression.

## Progression of arrhythmogenic cardiomyopathy disease

As expected, probands had more severe structural and functional abnormalities than family members both at inclusion and at last...
| Cardiac imaging | Inclusion (N = 144) | Follow-up (N = 144) | P |
|-----------------|---------------------|---------------------|---|
| **Major criteria** |                     |                     |   |
| Echocardiography, n (%) | 30 (21) | 64 (44) | <0.001 |
| Regional RV akinesia, dyskinesia or aneurysm and RVOT (plax) ≥ 32 mm (BSA corrected ≥ 19 mm/m²) or RVOT (psax) ≥ 36 mm (BSA corrected ≥ 21 mm/m²) measured at end-diastole or FAC ≤ 33% | | |
| Probands, n (%) | 27 (40) | 45 (66) | <0.001 |
| Family members, n (%) | 3 (4) | 19 (25) | <0.001 |
| CMR criteria, n (%) | 18 (13) | 23 (16) | 0.06 |
| Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and RV end-diastolic volume / BSA ≥ 110 mL/m² (male) or ≥ 100 mL/m² (female) or RV ejection fraction ≤ 40% | | |
| Probands, n (%) | 18 (26) | 21 (31) | 0.25 |
| Family members, n (%) | 0 (0) | 2 (3) | 0.50 |
| **Minor criteria** |                     |                     |   |
| Echocardiography, n (%) | 19 (13) | 23 (16) | 0.60 |
| Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and RVOT (plax) > 29 mm to ≤ 32 mm (BSA corrected ≥ 16 mm/m² to < 19 mm/m²) or RVOT (psax) ≥ 32 mm to < 36 mm (BSA corrected ≥ 18 mm/m² to < 21 mm/m²) measured at end-diastole or FAC > 33% ≤ 40% | | |
| Probands, n (%) | 1 (16) | 10 (15) | 1.00 |
| Family members, n (%) | 8 (11) | 13 (17) | 0.33 |
| CMR criteria, n (%) | 10 (7) | 12 (8) | 0.63 |
| Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and RV end-diastolic volume / BSA ≥ 100 to 110 mL/m² (male) or ≥ 90 to 100 mL/m² (female) or RV ejection fraction > 40% to ≤ 45% | | |
| Probands, n (%) | 6 (9) | 7 (10) | 1.00 |
| Family members, n (%) | 4 (5) | 5 (7) | 1.00 |
| Major tissue characterization criteria, n (%) | 2 (1) | 2 (1) | 1.00 |
| Residual myocytes < 60% by morphometric analysis (or < 50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy | | |
| Probands, n (%) | 1 (1) | 1 (1) | 1.00 |
| Family members, n (%) | 1 (1) | 1 (1) | 1.00 |
| **Electric criteria** |                     |                     |   |
| Repolarization abnormalities | | | |
| Major criteria, n (%), TWI in right precordial leads (V1, V2 and V3) | 40 (28) | 44 (31) | 0.48 |
| Probands, n (%) | 34 (50) | 36 (53) | 0.75 |
| Family members, n (%) | 6 (8) | 8 (10) | 0.73 |
| Any minor criteria, n (%), TWI in leads V1 and V2 or in V4, V5, and V6 | 15 (10) | 22 (15) | 0.12 |
| TWI in leads V1, V2, V3, and V4 with RBBB | | | |
| Probands, n (%) | 5 (7) | 10 (15) | 0.06 |
| Family members, n (%) | 10 (13) | 12 (16) | 0.75 |
| Depolarization criteria | | | |
| Major criteria, n (%), Epsilon wave in the right precordial leads (V1–V3) | 5 (4) | 18 (13) | <0.001 |
| Probands, n (%) | 5 (7) | 15 (22) | 0.002 |
| Family members, n (%) | 0 (0) | 3 (4) | 0.25 |
| Minor criteria, n (%), terminal activation duration ≥ 55msec | 18 (13) | 71 (49) | <0.001 |
| Probands, n (%) | 13 (19) | 37 (54) | <0.001 |
| Family members, n (%) | 5 (7) | 34 (45) | <0.001 |
| Arrhythmia criteria | | | |
| Major criteria, n (%), NSVT or VT of LBBB morphology with superior axis | 22 (15) | 27 (19) | 0.06 |
| Probands, n (%) | 22 (32) | 25 (37) | 0.25 |
| Family members, n (%) | 0 (0) | 2 (3) | 0.50 |
| Minor criteria, n (%), NSVT or VT of LBBB morphology with inferior axis or unknown axis | 32 (22) | 47 (33) | <0.001 |
| Probands, n (%) | 30 (44) | 40 (59) | 0.002 |

Continued
Table 2  Continued

| Cardiac imaging                      | Inclusion (N = 144) | Follow-up (N = 144) | P   |
|--------------------------------------|---------------------|---------------------|-----|
| Family members, n (%)                | 2 (3)               | 7 (9)               | 0.06|
| PVC count > 500/24 h<sup>c</sup>     | 27 (19)             | 32 (22)             | 0.06|
| Probands, n (%)                      | 15 (22)             | 19 (28)             | 0.12|
| Family members, n (%)                | 12 (16)             | 13 (17)             | 1.00|
| ICD, n (%)                           | 35 (24)             | 61 (42)             | <0.001|
| Probands, n (%)                      | 34 (50)             | 52 (76)             | <0.001|
| Family members, n (%)                | 1 (1)               | 9 (12)              | 0.008|

Values are frequencies (%). P-values are calculated by McNemars Test.
<sup>a</sup>CMR was performed in 94 patients at inclusion and in 15 patients at last follow-up.
<sup>b</sup>Holter monitoring was available in 85 patients at inclusion and in 97 patients at follow-up.

BSA, body surface area; CMR, cardiac magnetic resonance; FAC, fractional area change; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; NSVT, non-sustained ventricular tachycardia; plax, parasternal long axis view; psax, parasternal short axis view; PVC, premature ventricular complexes; RBBB, right bundle branch block; RV, right ventricular; RVOT, RV outflow tract; TWI, T-waves inversion; VT, ventricular tachycardia.

Table 3  Structural progression by 598 echocardiographic assessments in 144 patients with arrhythmogenic cardiomyopathy and mutation-positive family members

|                                | At inclusion (n = 144) | Progression rate, 1 year (SE) | At last follow-up (n = 144) | P for progression |
|--------------------------------|------------------------|-------------------------------|-----------------------------|-------------------|
| LVEF, %                        | 55 ± 7                 | 0.0 (0.06)                    | 55 ± 8                      | 0.99              |
| Probands, n = 309/68           |                        |                               |                             |                   |
| Family members, n = 289/76     | 58 ± 4                 | 0.1 (0.05)                    | 59 ± 5                      | 0.16              |
| P for interaction              |                        |                               |                             |                   |
| LVGLS, %                       | -18.3 ± 3.0            | 0.1 (0.02)                    | -17.2 ± 3.5                 | <0.001            |
| Probands, n = 309/68           |                        |                               |                             |                   |
| Family members, n = 289/76     | -19.9 ± 2.4            | 0.1 (0.03)                    | -19.4 ± 2.4                 | 0.01              |
| P for interaction              |                        |                               |                             |                   |
| RVFAC, %                       | 34 ± 8                 | -0.6 (0.05)                   | 31 ± 10                     | <0.001            |
| Probands, n = 309/68           |                        |                               |                             |                   |
| Family members, n = 289/76     | 44 ± 8                 | -0.8 (0.06)                   | 41 ± 7                      | <0.001            |
| P for interaction              |                        |                               |                             |                   |
| RVOT, mm                       | 37 ± 8                 | 0.5 (0.04)                    | 41 ± 7                      | <0.001            |
| Probands, n = 309/68           |                        |                               |                             |                   |
| Family members, n = 289/76     | 32 ± 5                 | 0.6 (0.04)                    | 36 ± 6                      | <0.001            |
| P for interaction              |                        |                               |                             |                   |
| RVD, mm                        | 46 ± 7                 | 0.8 (0.05)                    | 49 ± 10                     | <0.001            |
| Probands, n = 309/68           |                        |                               |                             |                   |
| Family members, n = 289/76     | 37 ± 5                 | 0.7 (0.05)                    | 41 ± 6                      | <0.001            |
| P for interaction              |                        |                               |                             |                   |
| RV EDV, mL                     | 163 ± 22               | -2.1 (3.53)                   | 192 ± 61                    | 0.55              |
| Probands, n = 16/8             |                        |                               |                             |                   |
| Family members, n = 12/6       | 164 ± 49               | 9.3 (1.75)                    | 197 ± 44                    | <0.001            |
| P for interaction              |                        |                               |                             |                   |
| RV EF, %                       | 51 ± 7                 | 0.1 (0.47)                    | 49 ± 9                      | 0.81              |
| Probands, n = 16/8             |                        |                               |                             |                   |
| Family members, n = 12/6       | 53 ± 10                | 0.3 (1.06)                    | 54 ± 5                      | 0.80              |
| P for interaction              |                        |                               |                             |                   |

Values at inclusion and last follow-up are mean ± SD. Yearly progression rate with standard errors, P-value for progression, and interaction are calculated by linear mixed model statistics with exchangeable covariance structure and random intercept.

n, imaging examinations/patients; LVEF, left ventricular ejection fraction; LVGLS, LV global longitudinal strain; RVD, RV basal diameter; RVFAC, right ventricular fractional area change; RVOT, RV outflow tract diameter; SE, standard error.
High penetrance and similar disease progression in AC probands and in family members

Importantly, however, structural disease progressed at a similar rate in probands and in family members. Although probands and family members are obviously diagnosed in different disease stages \(^{16}\) (Take home figure), we found no intergroup difference in structural progression expressed by the annual rate of change in imaging parameters.

Patients with AC are often followed serially with repeated echocardiograms. However, how to evaluate a clinically significant difference between these measurements is not well-defined. Our study is the first reporting the progression of continuous variables measured by echocardiography over a significant period of time in a large cohort of AC patients. Annual progression rate in imaging parameters may help to estimate follow-up intervals and management in AC patients in future studies. Deterioration of both RV and LV parameters supported the biventricular nature of the disease.

**Table 4** Cox regression of markers of first arrhythmic event (n = 14) from inclusion to last follow-up in 86 arrhythmogenic cardiomyopathy patients and mutation-positive family members without previous arrhythmias

| Marker                                          | Univariable HR (95% CI) | P     | Multivariable HR (95% CI) | P     |
|-------------------------------------------------|-------------------------|-------|---------------------------|-------|
| Female sex (yes vs. no)                         | 0.52 (0.18, 1.56)       | 0.24  | 1.02 (0.23, 4.50)         | 0.98  |
| Age at inclusion (years)                        | 0.99 (0.96, 1.02)       | 0.52  | 0.98 (0.93, 1.02)         | 0.29  |
| Proband status (yes vs. no)                     | 9.47 (2.97, 30.26)      | <0.001| 16.97 (2.90, 99.38)       | 0.002 |
| Structural progression (yes vs. no)             | 13.59 (1.67, 110.72)    | 0.02  | 21.24 (2.47, 182.81)      | 0.005 |
| Electrical progression (yes vs. no)             | 1.69 (0.42, 6.75)       | 0.46  |                           |       |

P-values by cox regression analyses. Multivariable HR is adjusted for sex, age at inclusion, and proband status. Structural progression was defined as the development of new echocardiographic diagnostic criteria during follow-up.

CI, confidence interval; HR, hazard ratio.

**Association between structural progression and first arrhythmic event**

Approximately 5% of family members experienced severe VA during 5 years of follow-up. Asymptomatic AC family members are the most challenging to decide on a primary prevention ICD. \(^{17}\) Structural progression was an important and independent marker of severe VA in our study and any development of structural abnormalities during follow-up may strengthen this decision. Furthermore, LV involvement should be assessed as any LV involvement further increase risk of arrhythmias. Previous reports showed associations between severe structural RV progression and VA in patients with definite AC diagnosis \(^{14,18}\) and we have recently shown that history of high-intensity exercise, T-waves inversions and increased LV MD predict life-threatening VA. \(^{6}\) In this study, we showed that high-intensity exercise and LV MD were associated with structural progression also in family members with no or mild structural changes at inclusion.
**Figure 3** Kaplan–Meier curves of survival free from first severe ventricular arrhythmic event in 86 AC patients and in mutation-positive family members only without history of arrhythmia at inclusion. Green curves represent presence and blue curves absence of structural progression during follow-up. First severe arrhythmic event was more frequent in patients with structural progression during follow-up in the total material (left panel) and in family members only (right panel).

**Take home figure** Arrhythmogenic cardiomyopathy disease progression. Probands and family members with arrhythmogenic cardiomyopathy had similar structural progression rates by linear mixed model statistical analysis of 598 repeated echocardiographic assessments in 144 individuals over 7 years follow-up. Structural progression was associated with higher incidence of first severe arrhythmic events.
Clinical implications

Arrhythmogenic cardiomyopathy family members detected by genetic screening should be followed closely since half of them may develop AC disease during the next 5 years even though they are without AC signs at first evaluation. Any structural changes detected in AC individuals who are not implanted with an ICD should raise the awareness of arrhythmic risk. The optimal frequency of repeated echocardiography may be individualized but should not be longer in family members than in probands due to similar disease progression.

Limitations

This was a repeated measures observational cohort study with associated limitations including the lack of causal inference. We conducted the study in a single tertiary reference centre, and the findings may not be valid in populations with other genetic and environmental demographics. Subgroup analyses were limited by small number of patients and events. Modern echocardiography is a precise tool, but structural progression can overlap with measurements variability. The definition of probands vs. family member is dependent on their first contact with the health system with possible influence on our results. Although patients affirmed moderation of exercise after AC diagnosis, we cannot exclude that they performed exercise which can have influenced our data.

Conclusion

Arrhythmogenic cardiomyopathy disease was evident in more than half of family members detected by genetic screening at first evaluation and half of family members without disease developed AC during 6 years of follow-up. Five per cent of family members had a first severe ventricular arrhythmic event during follow-up, emphasizing the high arrhythmic risk. Importantly, rate of progression of AC disease was similar in probands and family members and was associated with higher incidence of first severe arrhythmic event during follow-up. Detection of any structural or functional abnormality is important in AC family members to identify individuals at high risk of VA.

Supplementary material

Supplementary material is available at European Heart Journal online.

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High penetrance and similar disease progression in AC probands and in family members
Late cardiac erosion after percutaneous ventricular septal defect closure: a complication after ventricular septal defect device implantation

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Ventricular septal defects (VSDs) are the most common congenital cardiac malformations accounting for ~30% of congenital heart disease. Although open heart surgery is considered a standard treatment, catheter-based intervention is a promising alternative, associated with a lower incidence of myocardial injury, less blood transfusion, faster recovery, and shorter hospitalization. The most relevant complications of this intervention are residual shunt, device-related arrhythmia, vascular complications, haemolysis, valve dysfunction, and device embolization.

We present the histopathological workup of an intraoperative removed VSD Occluder (AmplatzerTM, Muscular VSD Occluder, 10 mm, Abbott) which had been implanted 8 months ago in a 2-year-old boy (9.1 kg, 71 cm) with complex pulmonary atresia and multiple VSDs. Reoperation was planned in order to treat tricuspid valve stenosis and to close the not yet supplied apical VSDs. Intraoperatively, a masked perforation was found in the area of the ventricle at the level of the VSD occluder after opening the pericardium (Panel A). During open heart surgery, the VSD Occluder was removed and histological examination was performed.

On gross examination, the Occluder Device was intact (Panel B). To the intraventricular side, no deposition of thrombus material was detected. The Occluder surface showed complete neoendothelialization without significant pseudointimal proliferation (Panel C). No signs of calcification or inflammation were noted. In the area of the left ventricular free wall, the device was covered only by a very thin tissue layer, <150 μm (Panel E). At the transition to the ventricular myocardium, a loosened tissue composite of myocytes with partly pyknotic nuclei was found (Panel F). (Panel A) Intraoperative surgical image showing the exposed occluder struts (arrow). (Panel B) Macroscopy of the explanted VSD Occluder showing the perforated device (arrow). (Panel C) Intraventricular side of the Occluder with thin endothelial coating. (Panels D–F) Overview of a longitudinal (D) section through the VSD Occluder. (E and F) Higher magnifications of Panel D (small boxes) demonstrating only a very thin (<150 μm) tissue layer over the device struts with a loosened tissue composite of myocytes with partly pyknotic nuclei (arrows).