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Monitoring of Myocardial Involvement in Early Arrhythmogenic Right Ventricular Cardiomyopathy Across the Age Spectrum

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ABSTRACT

BACKGROUND Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by fibrofatty replacement of primarily the right ventricular myocardium, a substrate for life-threatening ventricular arrhythmias (VAs). Repeated cardiac imaging of at-risk relatives is important for early disease detection. However, it is not known whether screening should be age-tailored.

OBJECTIVES The goal of this study was to assess the need for age-tailoring of follow-up protocols in early ARVC by evaluating myocardial disease progression in different age groups.

METHODS We divided patients with early-stage ARVC and genotype-positive relatives without overt structural disease and VA at first evaluation into 3 groups: age <30 years, 30 to 50 years, and ≥50 years. Longitudinal biventricular deformation characteristics were used to monitor disease progression. To link deformation abnormalities to underlying myocardial disease substrates, Digital Twins were created using an imaging-based computational modeling framework.

RESULTS We included 313 echocardiographic assessments from 82 subjects (57% female, age 39 ± 17 years, 10% probands) during 6.7 ± 3.3 years of follow-up. Left ventricular global longitudinal strain slightly deteriorated similarly in all age groups (0.1%-point per year [95% CI: 0.05-0.15]). Disease progression in all age groups was more pronounced in the right ventricular lateral wall, expressed by worsening in longitudinal strain (0.6%-point per year [95% CI: 0.46-0.70]) and local differences in myocardial contractility, compliance, and activation delay in the Digital Twin. Six patients experienced VA during follow-up.

CONCLUSIONS Disease progression was similar in all age groups, and sustained VA also occurred in patients aged >50 years without overt ARVC phenotype at first evaluation. Unlike recommended by current guidelines, our study suggests that follow-up of ARVC patients and relatives should not stop at older age. (J Am Coll Cardiol 2023;82:785–797) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

GLS = global longitudinal strain

LV = left ventricular

LVEF = left ventricular ejection fraction

RV = right ventricular

SCD = sudden cardiac death

TFC = Task Force Criteria

VA = ventricular arrhythmia

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable cardiomyopathy characterized by fibrofatty replacement of primarily the right ventricular (RV) myocardium, providing a substrate for potentially life-threatening ventricular arrhythmias (VAs).[1,2] Variable disease expression is found in familial ARVC,[3] ranging from sudden cardiac death (SCD) in young individuals to a lifelong absence of any phenotype. To prevent SCD in apparently healthy carriers of disease-causing genetic variants, early detection of potentially proarrhythmic tissue substrates is important to guide follow-up, antiarrhythmic treatment, and timing of implantable cardioverter-defibrillator implantation.

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ARVC has an age-related penetrance, whereby patients classically present in the third or fourth decade of life with symptomatic VAs.[3-7] However, with increased use of genetic testing for ARVC, carriers of a (likely) pathogenic variant across all age groups are recognized and included in extensive cardiac screening protocols, including noninvasive cardiac imaging examinations for detection of early disease. Presence and especially progression of functional abnormalities caused by structural disease of myocardial tissue is an important risk marker for occurrence of VA in ARVC.[8-13] It is, however, currently not known whether structural disease progression occurs in all age groups, hampering age-tailored follow-up protocols. In a position statement from 2010, it was suggested that serial screening of relatives can be stopped at the age of 50 to 60 years, due to completed penetrance.[14] Therefore, we hypothesized that structural progression in early-stage ARVC occurs in early life and midlife, and progression at age >50 years is limited.

Conventional echocardiographic measurements in combination with visual assessment of wall motion abnormalities, as described in the 2010 diagnostic task force criteria (TFC),[15] lack sensitivity for detection of early structural disease substrates in ARVC.[16,17] Over the past decade, echocardiographic deformation imaging has emerged as a valuable tool for both early detection and prognosis in ARVC.[8,9,18-22] In this study, we used echocardiographic deformation imaging for monitoring of myocardial disease progression in patients with early-stage ARVC. To create a link between myocardial function and tissue substrates, we combined these clinical deformation imaging data with a recently developed patient-specific computer simulation technology.[23] This technology was used to create a series of Digital Twins of each patient's heart, providing unique insight in the development of regional RV tissue properties underlying the regional myocardial deformation abnormalities. Insight in the evolution of tissue substrates of individual patients may aid better prediction of unfavorable outcome.

By using echocardiographic deformation imaging and the related patient-specific simulations of cardiac mechanics, we aimed to evaluate structural progression in different stages of life in order to assess the need for age-tailoring of follow-up protocols in early-stage ARVC.

METHODS

STUDY DESIGN AND POPULATION. We included a consecutive primary preventive cohort of ARVC patients and genotype-positive family members evaluated at Oslo University Hospital, Rikshospitalet, Norway, between 1997 and 2021 with at least 2 clinical evaluations. Part of this cohort was reported in previous follow-up studies in ARVC patients.[10,24] Patients with previous myocardial infarction and congenital heart disease were excluded. To focus on patients with early-stage structural disease, patients who met a major echocardiographic TFC at first evaluation were excluded. We also excluded patients who experienced sustained VA (defined as a documented history of sustained ventricular tachycardia, aborted cardiac arrest, or appropriated implantable cardioverter-defibrillator therapy) at or before first evaluation.

Clinical characteristics were recorded at first evaluation. Subjects were divided into 3 age groups (<30 years, 30-50 years, and ≥50 years) based on their age at first evaluation, either for complaints or for family screening. Time to first VA was recorded prospectively from time of inclusion. End of observation was cardiac transplantation, death, or last clinical follow-up by January 1, 2021.

All patients gave written informed consent. The study complied with the declaration of Helsinki and was approved by the Regional Ethical Committee of South-Eastern Norway.

ECHOCARDIOGRAPHY. All available complete echocardiographic examinations in sinus rhythm between inclusion and last clinical follow-up were analyzed. First evaluation was defined at the time of first echocardiography on compatible hardware (GE Vivid 7, E9, or E95, EchoPac 203, GE Vingmed). Presence of major echocardiographic TFC was determined at first evaluation for the purpose of patient selection. Left

ventricular ejection fraction (LVEF) was measured by Simpson's biplane method and speckle tracking deformation imaging of both the left ventricle (LV) and RV was performed in all examinations, according to previously described protocols.[18,21,25,26] We assessed segmental RV deformation patterns in an RV-focused 4-chamber view, whereby a single-wall tracing of the RV free wall was automatically divided into a basal, mid, and apical segment. Timing of pulmonary valve closure was assessed by Doppler traces in the RV outflow tract, obtained in the parasternal short-axis view. The following deformation parameters were measured in each segment: time to onset of shortening (or electromechanical interval), systolic peak strain, and the amount of postsystolic shortening. These parameters were used to classify patients into 3 subgroups, each presenting with a distinct RV deformation pattern as described in previous studies.[11,19] In brief, a type I pattern is normal deformation; a type II pattern is characterized by delayed onset of shortening, reduced systolic peak strain, and minor postsystolic shortening; and a type III pattern is characterized by little or no systolic peak strain, predominantly systolic stretching, and major postsystolic shortening (**Central Illustration**, right upper panel). The LV global longitudinal strain (GLS) was calculated as the peak negative strain from the averaged regional 16-segment LV model.[21] RV free wall longitudinal strain was defined as the peak negative strain from the averaged regional RV free wall deformation characteristic. All measurements were performed by a single observer (Dr Kirkels) blinded to clinical information.

COMPUTATIONAL SIMULATIONS. To gain more insight into the course of myocardial disease development in individual patients, we created Digital Twins of the patient's heart at each follow-up, using our previously developed modeling framework.[23] In brief, this framework uses the patient's imaging data to personalize the well-established closed-loop CircAdapt model of the human heart and circulation.[27] This results in a series of patient-specific simulations of regional cardiac mechanics and global hemodynamics for each patient.

Besides LV and RV deformation data, this framework uses LV end-diastolic volume, LVEF, and RV end-diastolic diameter as input. Taking measurement uncertainty into account, the estimated tissue properties are represented as a probability distribution. Three myocardial tissue properties were estimated for each RV segment: contractility, compliance, and mechanical activation delay. Given the interindividual differences in biometrics and loading conditions, we focused on regional heterogeneity of estimated myocardial tissue properties rather than on absolute values. In brief, segmental contractility was defined as the maximum rate of active stress rise, which can be seen as the local tissue-level equivalent of the maximum rate of ventricular systolic pressure rise (dP/dt_{max}). Segmental wall compliance was defined as the slope of the end-diastolic myofiber stress-strain relationship at time before first ventricular activation and can be interpreted as the regional tissue equivalent of the slope of the end-diastolic pressure-volume relation. Mechanical activation delay was defined as the time interval between the model's intrinsic time of activation and the onset of local active stress development.[23]

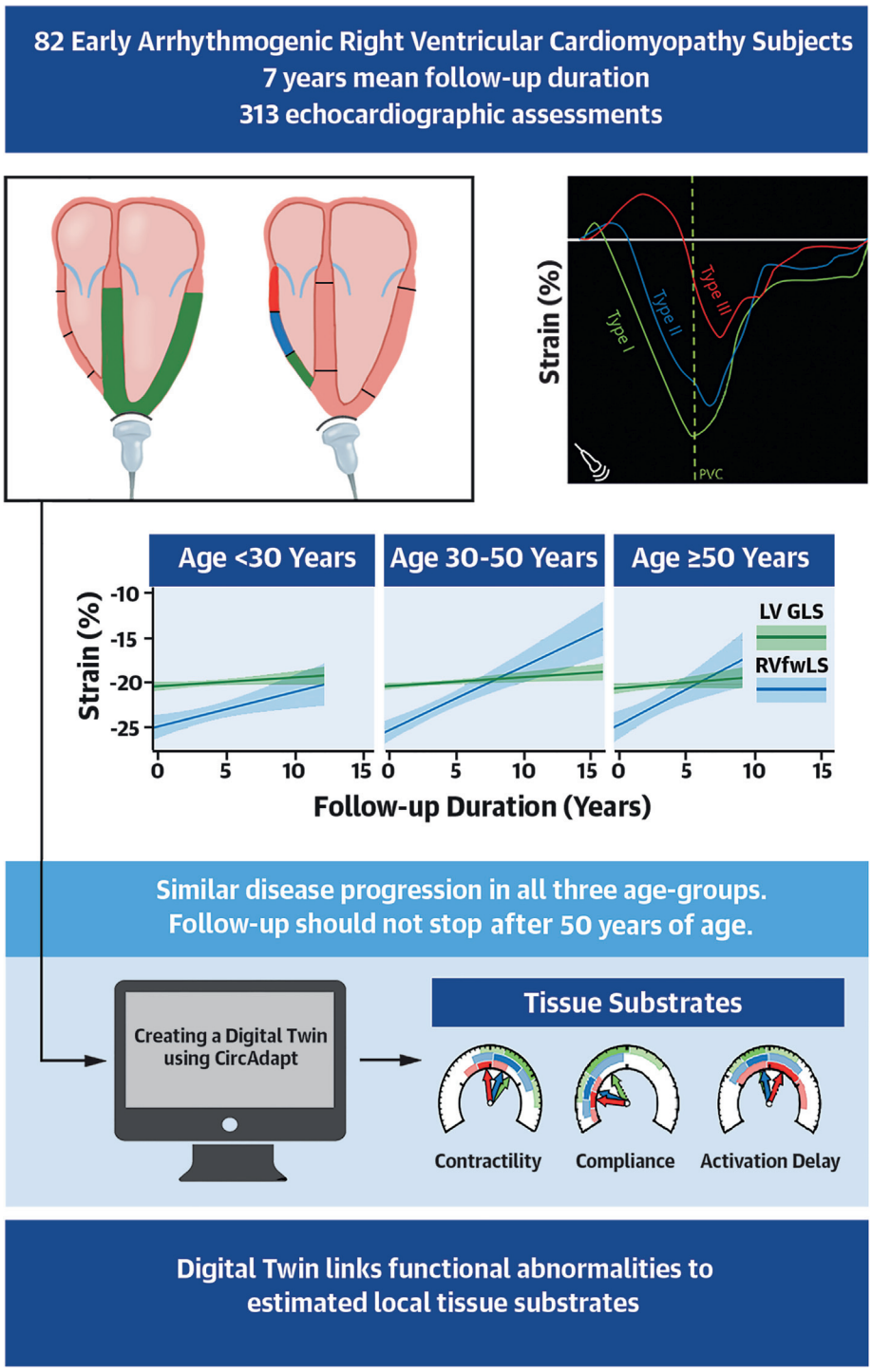
STATISTICAL ANALYSIS. Statistical analyses were performed using IBM SPSS 26.0 (IBM Corp) and Stata SE 16.1 (StataCorp LLC). Values were expressed as mean ± SD or median (IQR), as appropriate, and were compared by Fisher exact test for dichotomous variables and Kruskal-Wallis test for continuous variables. After visually excluding the possibility of nonlinear trends, we assessed progression in the 3 age groups by entering the echocardiographic deformation parameters into a linear mixed model regression with exchangeable covariance structure and random effects at individual level. *P* values were 2-sided, and values <0.05 were considered significant.

RESULTS

CLINICAL CHARACTERISTICS. We included 82 early-stage ARVC patients and genotype-positive family members (57% female, age 39 ± 17 years, 10% probands) (**Table 1**). Of 192 eligible patients, 110 were excluded due to VA or major structural TFC at or before first echocardiographic examination, or absence of a follow-up examination (Supplemental Figure 1). A (likely) pathogenic variant was found in 92% of patients, mostly located in the plakophilin-2 gene (84%). During a mean follow-up time of 6.7 ± 3.3 years, 355 echocardiograms were performed (average of 4 examinations per patient [range 2-9 examinations per patient]). Forty-two examinations were excluded due to inadequate visualization of 1 or more RV free wall segments (n = 33), unavailability of raw echo data for deformation analysis (n = 7), or irregular heart rhythm (n = 2), leaving 313 examinations appropriate for analysis.

During follow-up, 6 patients experienced a first sustained VA, after a mean of 4.1 years (range 0.2-8.9 years). The mean age at event was 47 years (range 33-65 years).

CENTRAL ILLUSTRATION **Monitoring Age-Related Penetrance in Arrhythmogenic Right Ventricular Cardiomyopathy**



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Patients with early arrhythmogenic right ventricular cardiomyopathy (ARVC) and genotype-positive family members are frequently screened for structural abnormalities that are strongly associated with life-threatening ventricular arrhythmias. To find out whether this extensive screening can be stopped at older age, we performed biventricular deformation analyses in 313 longitudinal echocardiograms of 82 early ARVC patients and family members at risk divided over 3 age groups. Digital Twins of the patients' hearts were created to reveal the local tissue substrates underlying myocardial deformation abnormalities. We found similar patterns of progression in both young, middle-aged, and older subjects and first life-threatening arrhythmias still occurred in patients aged >50 years, suggesting that follow-up of early ARVC patients and family members should not stop at older age. LV GLS = left ventricular global longitudinal strain; RVfwLS = right ventricular free wall longitudinal strain.

PROGRESSION OF DEFORMATION ABNORMALITIES. Both global (Figure 1) and segmental (Figure 2) deformation characteristics deteriorated during follow-up in all 3 age groups. Deterioration in LVEF was not observed in any of the age groups (−0.03% per year [95% CI: −0.16% to 0.09% per year]). However, LV function measured by LV GLS deteriorated slightly in all 3 age groups by an average of 0.1%-point per year (95% CI: 0.05%-0.15%-point per year). Deterioration was more pronounced in the RV lateral wall in all age groups, expressed by a mean worsening in RV free wall longitudinal strain of 0.6%-point per year (95% CI: 0.46%-0.70%-point per year). The 3 segmental deformation characteristics used to classify RV deformation type showed that the basal segment was most impaired in all age groups, whereby an apex-to-base gradient was maintained during follow-up (Figure 2). When displaying progression of the deformation types during follow-up (Figure 3), the deformation pattern of the basal segment was most frequently impaired (type II or III). Progression to a more abnormal deformation pattern occurred in all age groups, whereby the pattern in the basal segment deteriorated in approximately one-half of the cases and in the mid segment in approximately one-third. Even in some subjects >50 years of age with normal RV deformation at first evaluation, progression toward abnormal deformation patterns was evident. Deformation in the apical segment was normal in most cases, and progression to an abnormal apical deformation pattern was rare. Yearly progression rates and mean values at inclusion and last follow-up are provided in Supplemental Table 1.

When focusing on fulfillment of the 2010 TFC,[15] 16 subjects progressed toward a minor or major criterion for structural abnormalities during follow-up. All but 1 already showed abnormal deformation patterns before or at the moment of TFC adjudication.

DEFORMATION CHARACTERISTICS OF PATIENTS WITH VA. The 6 patients who experienced sustained VA during follow-up all showed abnormal RV deformation patterns at first evaluation. In the basal segment of the RV free wall, 4 patients showed a type II pattern and 2 patients showed a type III pattern. During follow-up, all of them progressed to a type III pattern. The small size of this subgroup prevents comparative analyses between subjects with and without VA during follow-up.

PROGRESSION OF MODELED RV TISSUE PROPERTIES. To illustrate the application of longitudinal monitoring of myocardial disease on a patient-specific level, we first provide 2 representative case studies of subjects included in the cohort.

TABLE 1 Baseline Characteristics of 82 ARVC Patients and Family Members, Comparing 3 Different Age Groups

	Total (N = 82)	Age <30 y (n = 27)	Age 30-50 y (n = 32)	Age ≥50 y (n = 23)	*P* Value
Age, y	39 ± 17	20 ± 6	39 ± 6	60 ± 7	
Female	47 (57)	15 (56)	20 (63)	12 (52)	0.723
Proband	8 (10)	0 (0)	4 (13)	4 (17)	0.064
Follow-up time, y	6.5 ± 3.1	7.1 ± 2.9	6.9 ± 3.5	5.2 ± 2.5	0.109
VA during follow-up	6 (7)	0 (0)	4 (13)	2 (9)	0.197
(Likely) pathogenic variant	75 (92)	27 (100)	29 (91)	19 (83)	0.077
PKP2	69 (84)	24 (89)	28 (88)	17 (74)	0.326
DSG2	5 (6)	2 (7)	1 (3)	2 (9)	0.616
DSP	1 (1)	1 (4)	0 (0)	0 (0)	0.610

Values are mean ± SD or n (%).
DSG2 = desmoglein-2 gene; DSP = desmoplakin gene; PKP2 = plakophilin-2 gene; VA = life-threatening ventricular arrhythmia.

Patient 1 was a 20-year-old woman followed in the outpatient department for 4.3 years (Figure 4A). At first evaluation, RV deformation was already slightly abnormal in the basal segment. During follow-up, the deformation pattern of especially the basal segment and to a lesser extent the mid segment became increasingly abnormal with strongly reduced peak strain. In the Digital Twin, it was estimated that the heterogeneity relied on mostly reduced contractility and only slightly on reduced compliance.

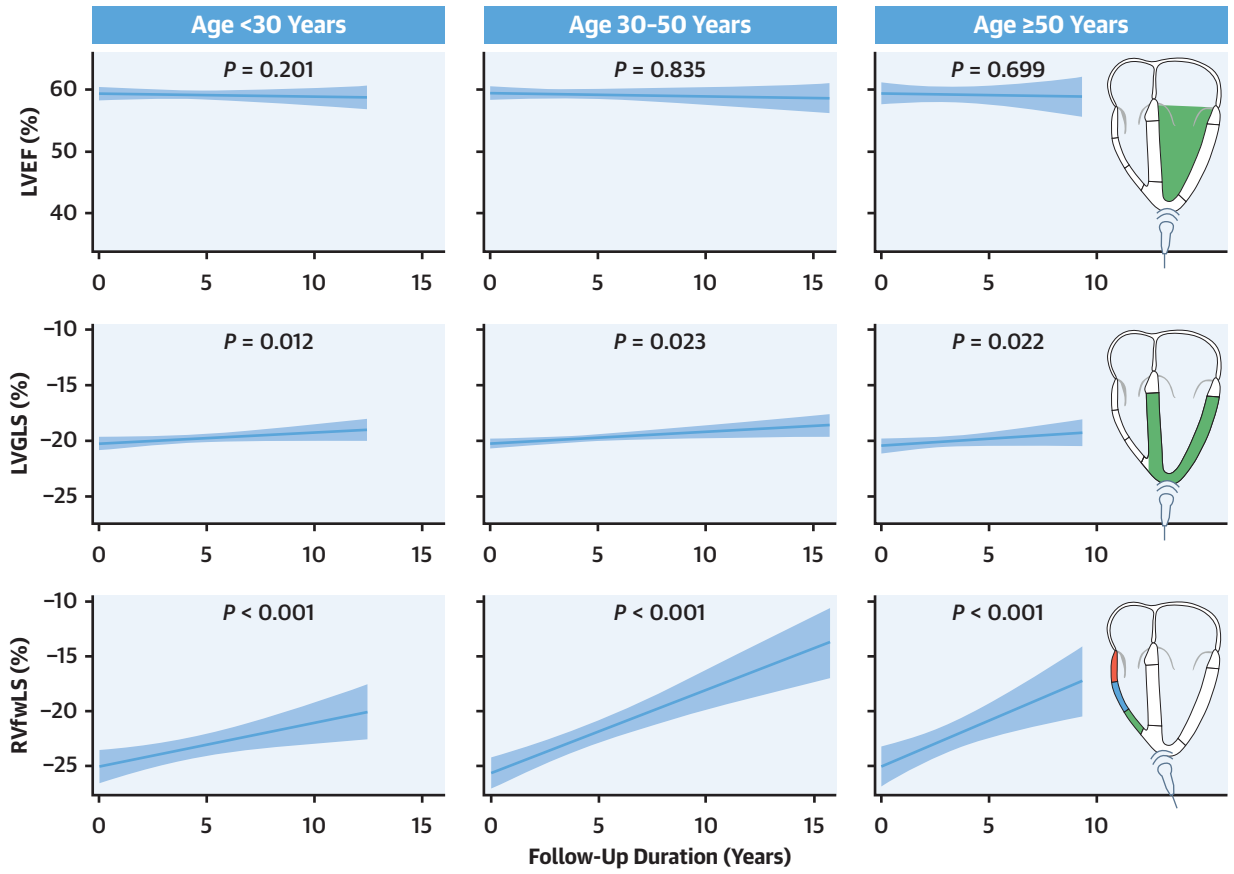
Patient 2 was a 36-year-old woman who experienced sustained VA 2.9 years after first evaluation (Figure 4B). During the first examination, RV deformation was slightly abnormal in the basal segment, with delayed onset of shortening, slightly reduced peak strain, and mild postsystolic shortening. During follow-up, deformation patterns became increasingly abnormal in all RV segments, whereby the basal pattern was most affected. This apex-to-base heterogeneity was expressed in the tissue substrate in the Digital Twin as well. Heterogeneity in estimated RV tissue properties was first observed in the activation delay and later also in contractility and compliance.

The increasing heterogeneity of estimated tissue properties within the RV free wall was also evident on a group level in all 3 age groups (Figure 5, Supplemental Table 2).

DISCUSSION

By monitoring myocardial disease progression in early ARVC, we found that LV GLS slightly deteriorated and especially RV deformation abnormalities progressed over time in all investigated age groups. Digital Twins of the patients' hearts were created to

FIGURE 1 Global Myocardial Disease Progression

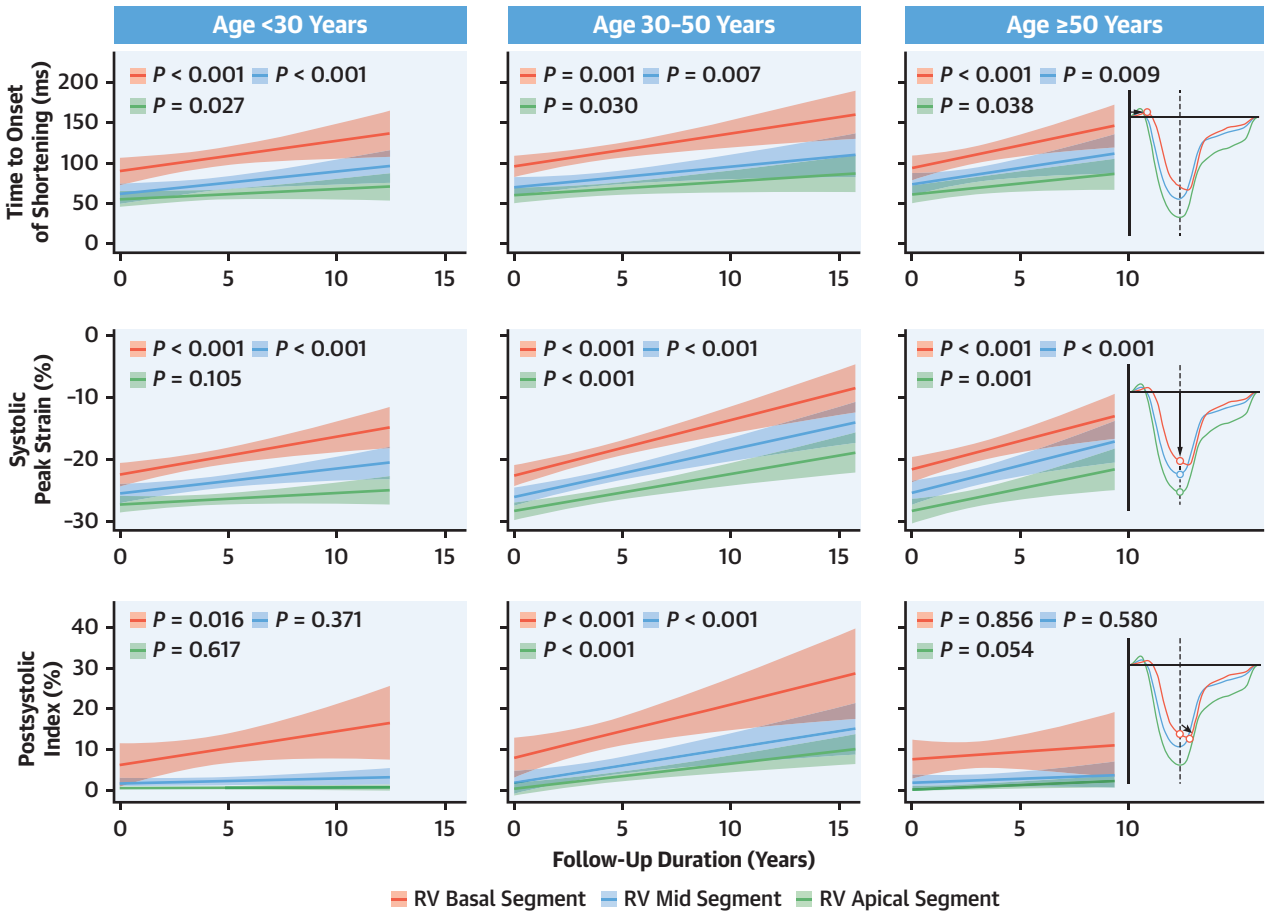


Progression of left ventricular ejection fraction (LVEF), left ventricular global longitudinal strain (LVGLS), and right ventricular free wall longitudinal strain ($RV_{FW}LS$), separated by age group. *P* values are for progression during follow-up. Deterioration in LVEF was not observed in any of the age groups, but LV function deteriorated by absolute 0.1%-point per year (95% CI: 0.05%-0.15%-point per year) worsening of GLS. Deterioration was faster in the right ventricular lateral wall, expressed by a mean worsening of absolute 0.6%-point per year (95% CI: 0.46%-0.70%-point per year) (Supplemental Table 1).

link deformation abnormalities to underlying myocardial disease substrates, revealing local differences in contractility, compliance, and mechanical activation delay. Based on our findings, age-based tailoring of follow-up intervals would not be indicated. On the contrary, progression continued throughout all age groups and was in multiple cases followed by sustained VA, indicating the need for lifelong follow-up.

PROGRESSION OF DEFORMATION ABNORMALITIES. Our study showed that deformation imaging is a useful technique for monitoring of myocardial disease progression in ARVC. In a previous study on serial evaluation of ARVC relatives, one-third showed electrical progression during a 4-year follow-up and structural progression was rare.[28] However, structural progression was measured by increase in 2010 TFC, which lacks sensitivity for detection of early disease manifestation.[17] We have previously shown that deformation imaging is superior for detection of early disease as compared with 2010 TFC.[29] Deformation analyses in the current study showed that abnormalities were often present before fulfillment of structural 2010 TFC. Progression of abnormalities occurred in all 3 age groups in both the LV and RV, but progression was more pronounced in the RV. This is in line with expectations, because primarily the RV myocardium is affected by fibrofatty replacement in ARVC.[1,2] From **Figure 3** it can be appreciated that RV deformation types are a robust

FIGURE 2 **Segmental Myocardial Disease Progression**



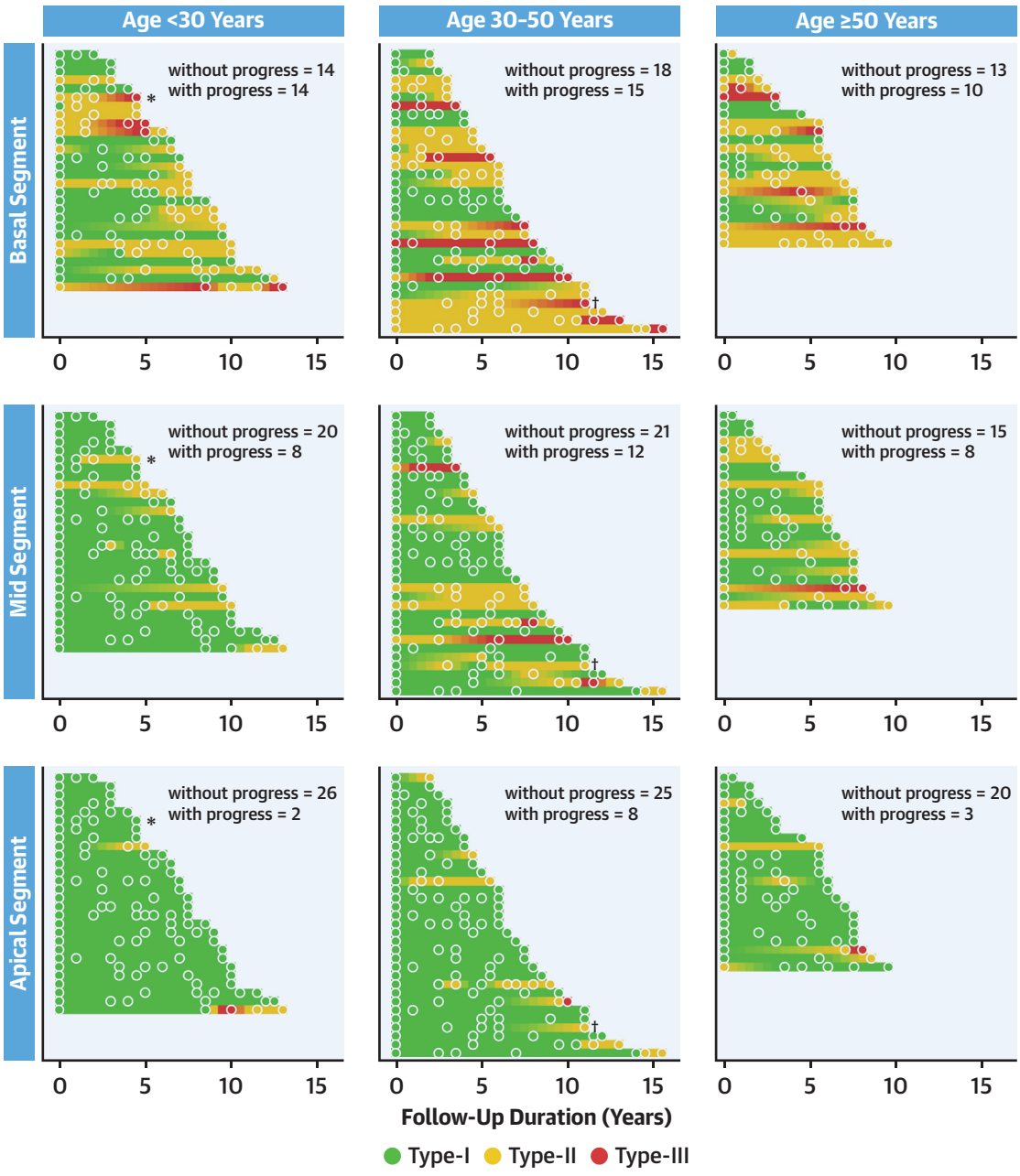
Progression of segmental deformation parameters of the right ventricle (RV), separated by age group. *P* values are for progression during follow-up. The basal segment was most impaired in all age groups, whereby an apex-to-base gradient was maintained during follow-up (Supplemental Table 1).

classification method during serial analyses, enabling detection of disease progression over time. This confirms that once abnormal, RV deformation patterns remain abnormal, as was previously shown in another cohort of ARVC patients with 2 sequential echocardiographic examinations.[30] Our segmental analysis consistently showed that all deformation parameters were worse in the basal segment and progressed over time from base to apex. This is in line with previous studies in other cohorts, which showed that the subtricuspid segment of the RV lateral wall is the earliest and most severely affected area in ARVC.[11,19,30,31]

It is conceivable that longitudinal strain also slightly deteriorates over time in healthy individuals. Although this has been shown for LV GLS,[32] the deterioration is small and probably not clinically relevant in the RV free wall.[33] Importantly, the prolonged time to onset of shortening and postsystolic shortening, as observed in ARVC patients, are not observed in physiologic aging of the myocardium.

PROGRESSION OF RV TISSUE SUBSTRATES. Definitive diagnosis of ARVC is based on the presence of transmural fibro-fatty replacement of RV myocardium at biopsy, autopsy, or surgery.[2,34] Because histology is not available in the vast majority of patients, TFC guide the diagnosis of ARVC.[15] The use of personalized computational modeling can give more insight into the patient's underlying myocardial disease

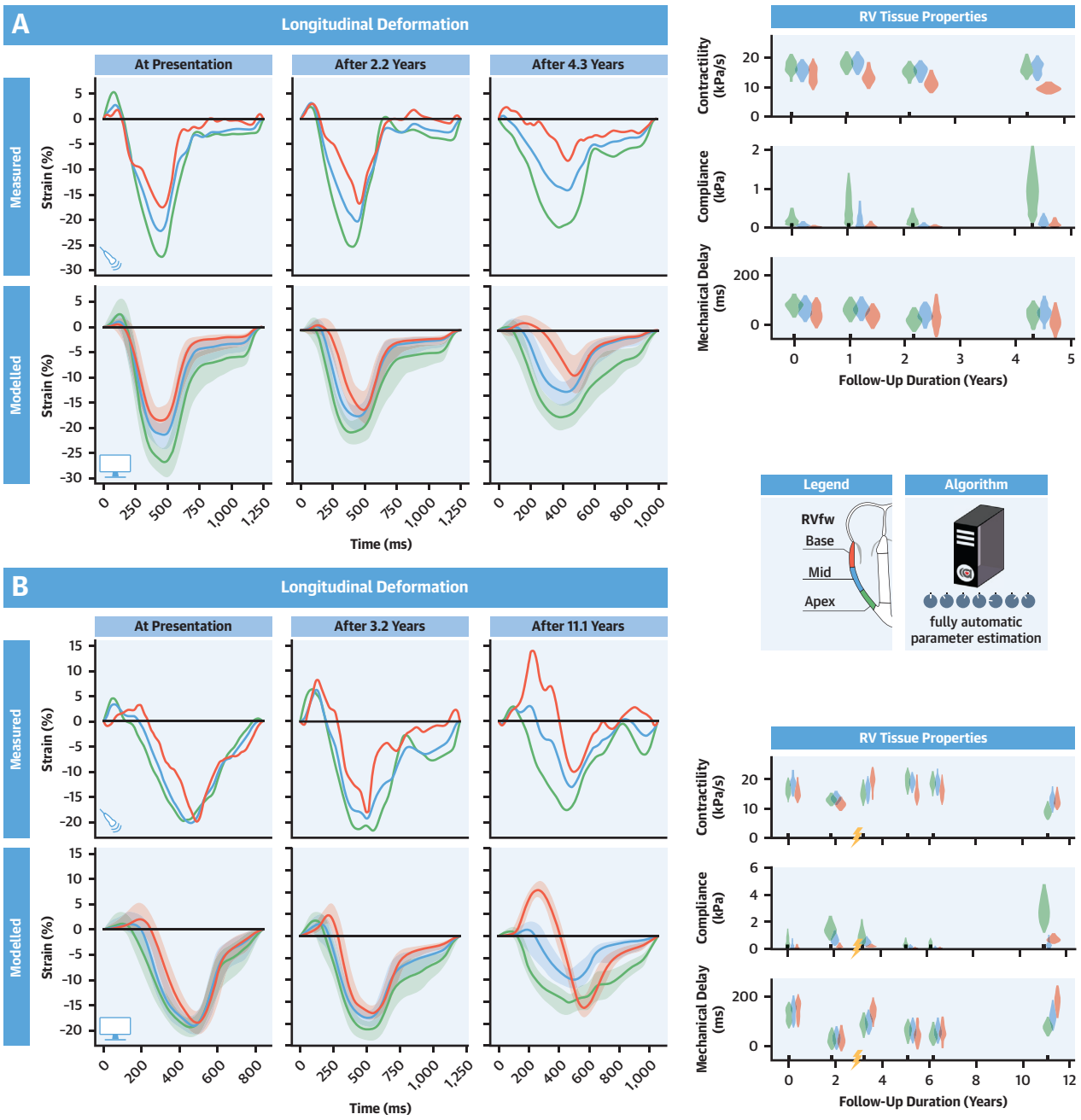
FIGURE 3 **Progression of RV Deformation Patterns**



Progression of right ventricular (RV) deformation types in the 3 RV free wall segments, separated by age group. The deformation pattern of the basal segment was most frequently impaired (type II or III). Progression to a more abnormal deformation pattern occurred in all age groups, whereby the pattern in the basal segment deteriorated in approximately one-half of the cases and in the mid segment in approximately one-third. Deformation in the apical segment was normal in most cases, and progression to an abnormal apical deformation pattern was less likely. *Case study 1 as displayed in Figure 4. †Case study 2 as displayed in Figure 4.

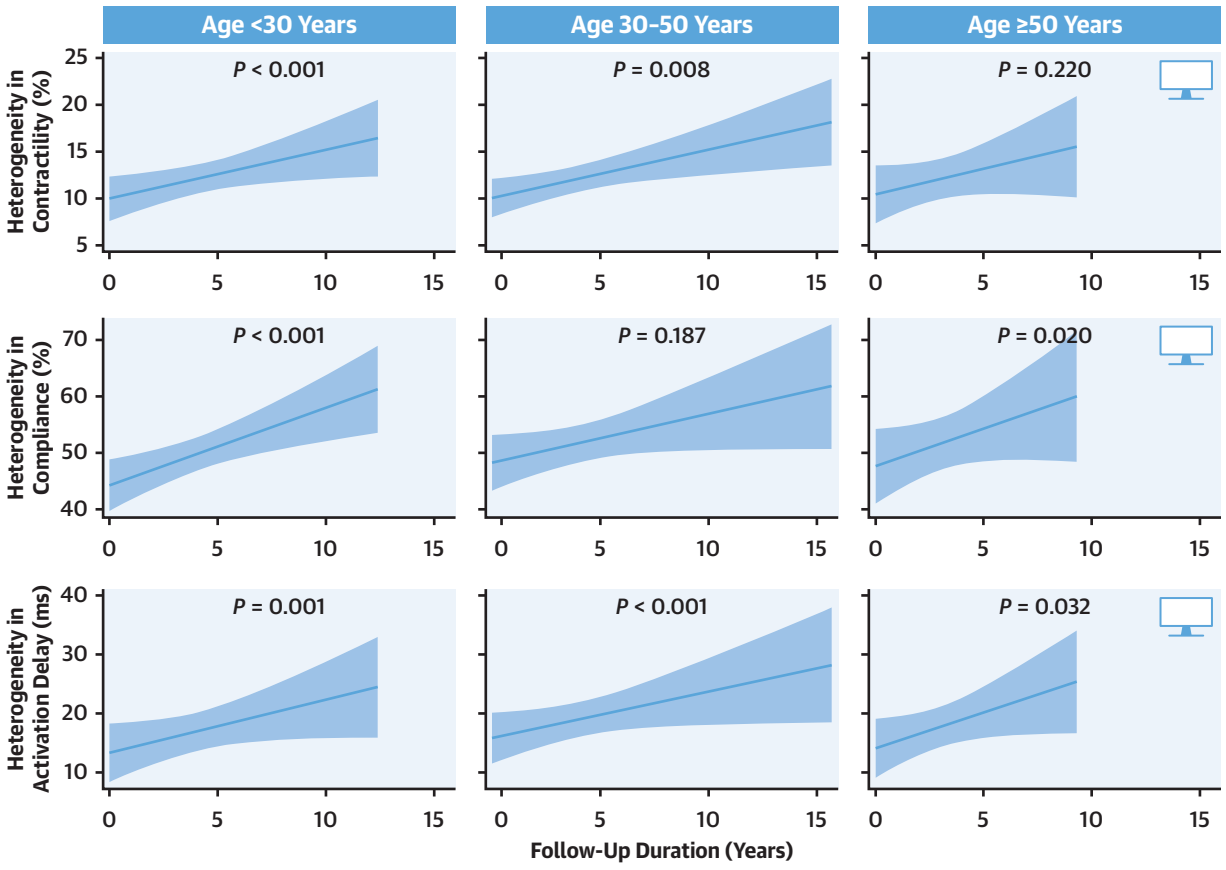
substrate through the estimated tissue properties being directly related to intrinsic myocardial function and composition.[20,23,35] In the current study, we applied this Digital Twin approach on serial echocardiographic examinations in a large cohort to gain insight into the evolution of early myocardial disease substrates in ARVC. On a group level, we found increasing heterogeneity of both contractility,

FIGURE 4 Myocardial Disease Progression in 2 Patients With Early ARVC



(A) Case study 1. This 20-year-old patient was followed in the outpatient department for 4.3 years. At first evaluation, right ventricular (RV) deformation was slightly abnormal in the basal segment. During follow-up, the deformation pattern of especially the basal segment and to a lesser extent the mid segment became increasingly abnormal with strongly reduced peak strain. In the Digital Twin, it was estimated that the heterogeneity relied on mostly reduced contractility and a little reduced compliance. **(B)** Case study 2. This 36-year-old patient experienced a sustained ventricular arrhythmia 2.9 years after the first evaluation **(yellow lightning bolt)**. During the first examination, RV deformation was slightly abnormal in the basal segment, with delayed onset of shortening, slightly reduced peak strain, and mild postsystolic shortening. During follow-up, deformation patterns became increasingly abnormal in all RV segments, whereby the basal pattern was most affected **(Measured** row of panels in **A** and **B)**. The apex-to-base heterogeneity was also expressed in the estimated RV tissue properties in the Digital Twin **(panels on the right)**. Heterogeneity was first observed in the mechanical activation delay and later also in contractility and compliance. ARVC = arrhythmogenic right ventricular cardiomyopathy; RVfw = right ventricular free wall.

FIGURE 5 Progression of Myocardial Disease Substrates in the Digital Twin



Progression of heterogeneity in estimated right ventricular (RV) tissue properties between the 3 RV free wall segments, separated by age group. A clear increase in heterogeneity was seen for all estimated RV tissue properties in the different age groups (Supplemental Table 2).

compliance, and activation delay in all 3 age groups, indicating the progression of local RV tissue substrates. We presented 2 case studies of patients from the cohort. The first (Figure 4A) showed progression of deformation abnormalities, which were, according to estimations in the Digital Twin, caused by decreased contractility and to a lesser degree decreased compliance. The patient had no VA during follow-up. In the second case (Figure 4B), the patient experienced VA while having no overt structural phenotype according to conventional TFC. RV deformation abnormalities preceded the arrhythmic event and heterogeneity was most pronounced in the activation delay. These cases illustrate the potential use of the modeling approach on a patient-specific basis, as specific estimated tissue abnormalities that are present before an arrhythmic event may have predictive value. The number of events in this study on subjects with early-stage ARVC was, however, too low to draw any firm conclusions from these findings.

CLINICAL IMPLICATIONS. Prevention of SCD is the most important goal of ARVC screening. Prior studies report SCD rates up to 23% at presentation, mainly in young ARVC patients.[3,4] Cascade genetic screening provides clinicians with an increasing group of patients at risk of severe arrhythmic events, but without an overt phenotype at first evaluation. Because there is a clear correlation between structural disease expression and the risk of arrhythmias, these patients undergo frequent cardiac evaluations to detect early signs of disease penetrance. A recent expert consensus statement recommended clinical evaluation of relatives at risk with 12-lead electrocardiogram, ambulatory electrocardiogram, and cardiac imaging every 1 to 3 years starting at 10 to 12 years of

age.[7] In a cohort study of ARVC patients who presented at ≥50 years of age, ventricular tachycardia and preexisting structural abnormalities were common, but SCD was not observed during follow-up.[5] The latter raises the question at what age can you stop the frequent and demanding screening of ARVC patients and relatives. In a position statement from 2010, it was suggested that serial screening of relatives can be stopped at the age of 50 to 60 years, due to completed penetrance.[14]

Although *conventional* echocardiographic TFC lack sensitivity for detection of early disease substrates,[28,29] this study supports the use of *deformation imaging* as a robust method for monitoring of ARVC patients and family members in the outpatient department. Our study showed similar patterns of myocardial disease progression in young, middle-aged, and older patients without an overt structural ARVC phenotype at first evaluation. These findings contradict the statement of completed penetrance after 50 years of age and do not support age-tailoring of cardiac imaging follow-up intervals at the outpatient department. Because other studies reported low risks of SCD in older relatives, structural progression in this group may be less alarming when compared with progression in younger relatives. However, of the 6 cases in which progression was followed by VA, 2 experienced a first event at the age of 64 and 65 years.

Deformation imaging provides an important additional tool for detection of ARVC disease manifestation and progression in an early stage, but always should be used in a multimodality setting, as described in the 2019 expert consensus statement.[7] When adhering to the recommended follow-up interval of 1 to 3 years, normal RV deformation can support clinicians in applying the longer interval, whereas development of deformation abnormalities can be a warrant to reevaluate the patient earlier.

Based on deformation imaging characteristics, the Digital Twin can translate myocardial behavior to valuable information on regional tissue properties. This potentially can be used to individualize risk assessment and to link genotype to phenotype. We have developed this method in subjects at risk of ARVC, but in the current era in which family screening and genetic testing are increasingly performed, deformation imaging[36] and Digital Twins can be easily applied in other cardiomyopathies as well.

STUDY LIMITATIONS. The single-center design was a limitation to this study. Because of the high prevalence of patients with (likely) pathogenic variants in the plakophilin-2 gene, the generalizability to patient populations with other dominating variants is uncertain. Future multicenter cohort studies should perform a genotype-specific approach to test the generalizability to, for instance, desmoplakin gene variant carriers, in which LV disease manifestation is often more pronounced.[7]

Because we excluded patients with overt structural disease or sustained VA at first evaluation, our cohort had a lower event rate than the average ARVC cohort. This resulted in a group of 6 patients who experienced sustained VA during follow-up, which is insufficient to search for risk factors in deformation imaging or estimated tissue properties on a group level.

CONCLUSIONS

ARVC disease progressed similarly in all age groups of patients presenting with early ARVC disease during 7 years of follow-up. We created Digital Twins of the patients' hearts to link deformation abnormalities to underlying myocardial disease substrates, revealing local differences in contractility, compliance, and mechanical activation delay. Potentially life-threatening arrhythmias also occurred in patients aged >50 years without overt ARVC phenotype at first evaluation, with the oldest patient aged 65 years. Contradicting previously published statements, our study suggests that follow-up of ARVC patients and family members should not stop at older age.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with ARVC, fibrofatty replacement of RV myocardium progresses similarly across the age spectrum, and the initial presentation of life-threatening arrhythmias may emerge at any age, suggesting that clinical surveillance of patients with ARVC and their family members should not stop at older age.

TRANSLATIONAL OUTLOOK: The use of cascade genetic screening is exposing an expanding population at risk of ARVC, and echocardiographic deformation imaging is useful for monitoring of disease progression. Insight into the evolution of tissue substrates of individual patients may improve prediction of adverse outcomes.

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KEY WORDS arrhythmogenic cardiomyopathy, ARVC, deformation imaging, Digital Twin, early detection, family screening

APPENDIX For supplemental tables and a figure, please see the online version of this paper.