Case Reports

Don't Always Blame CREST Syndrome for Heart Problems

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Abstract

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a non-ischemic cardiomyopathy predominantly affecting the right ventricle (RV) that leads to ventricular arrhythmia, sudden cardiac death, and heart failure. ARVC should be suspected in patients with RV cardiomyopathy without evidence of ischemia or pulmonary hypertension.

Case Report

A 43-year-old Caucasian man with history of limited cutaneous systemic sclerosis (lcSSc) CREST syndrome, chronic back pain, and bilateral hip replacement, presented after a witnessed convulsive syncopal episode. He reported no prior history of seizures, pre-syncope, syncope, palpitations, or chest pain. He denied nausea, vomiting, diarrhea, recent trauma, and changes in medications.

His family history was notable for cardiac disease: father with stents at age 61, paternal grandmother with myocardial infarction (MI) and sudden cardiac death at age 40, mother (deceased, age 48) with stents and coronary artery bypass graft in her 30s, maternal aunt with stents, maternal uncle with MI and sudden cardiac death in his 50s, maternal cousin with MI at age 44, and a sister with chest pain at age 46 resulting in a stress test and catheterization.

The patient initially presented to an outside hospital's emergency department and was tachycardic (101 bpm). The initial workup was negative for MI, pulmonary embolism, and intracranial hemorrhage. An echocardiogram revealed normal sinus rhythm premature atrial contractions, and prolonged QTc (518 ms). After he was transferred to our institution, he was afebrile and hemodynamically stable. The physical exam was notable only for sclerodactyly and calcinotic deposits on the fingers and elbows bilaterally. The cardiopulmonary exam was within normal limits and there were no focal neurological deficits.

An MRI scan of the brain was negative. Another echocardiogram revealed normal sinus rhythm with premature atrial contractions and T-wave inversions in V1-V4, along with epsilon waves in V1 (Figure 1).

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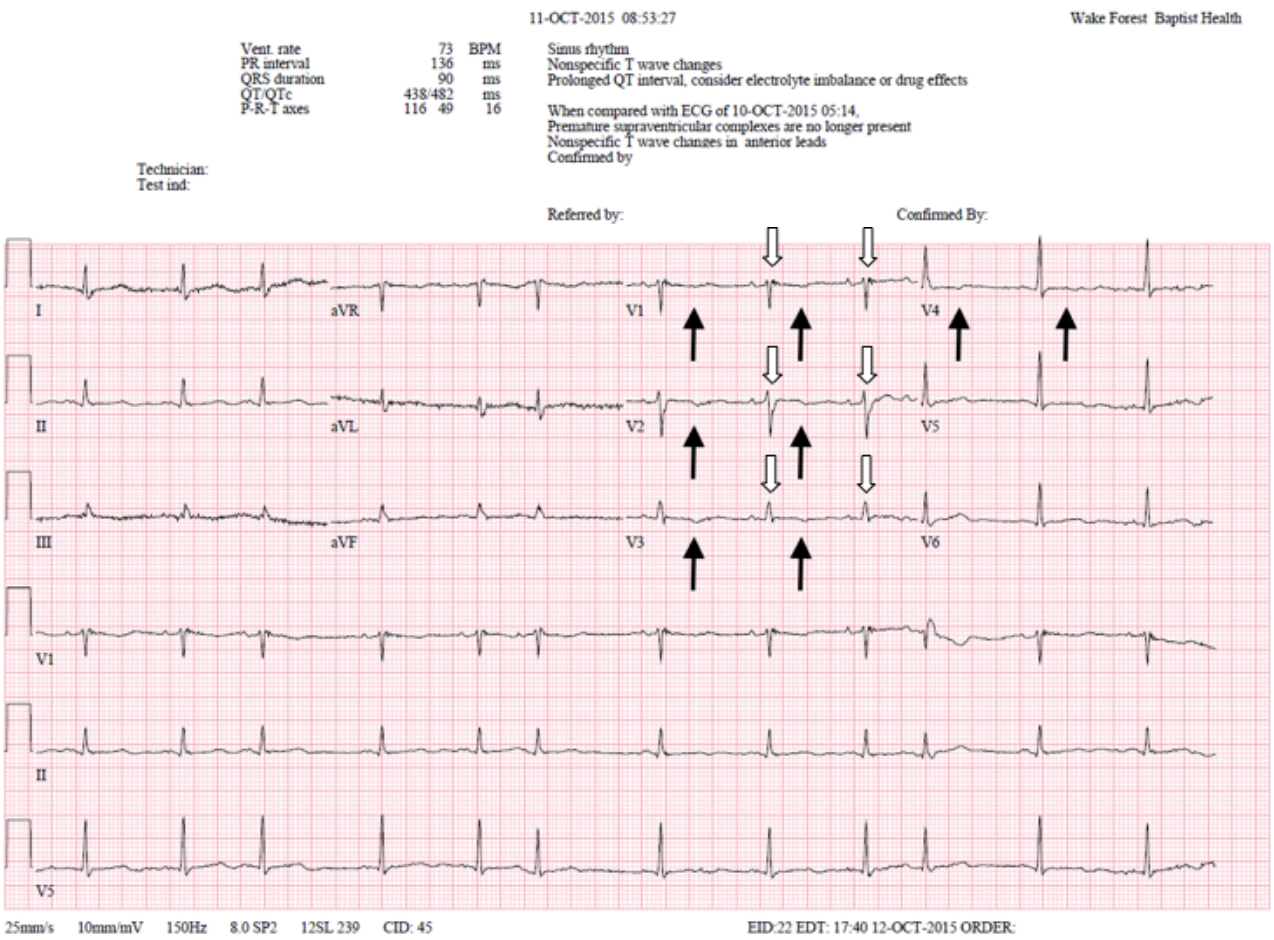

Figure 1: EKG revealed NSR, QTc 482 ms, and T-wave inversions in V1-V4 (black arrows), epsilon waves in V1-V3 (white arrows)

Table 1. Summary of results: transthoracic echocardiogram	
Left ventricle	Normal size and wall thickness Ejection fraction 55-60% No filling pattern or wall motion abnormalities
Right ventricle	Mildly dilated Mild-moderate reduced systolic function Right ventricle sinus pressure 18 mm Hg
Left atrium	Mildly dilated
Right atrium	Normal size
Aortic valve	Structurally normal and no aortic regurgitation
Mitral valve	Normal leaflet appearance and trace mitral regurgitation
Tricuspid valve	Structurally normal and trace tricuspid regurgitation
Pulmonic valve	Not well visualized and trace pulmonic regurgitation
Aortic root	Normal size
Pulmonary venous flow pattern	Normal
Inferior vena cava	Normal size
Pericardial effusion	None
FINAL ASSESSMENT	Abnormal right ventricular function, exclude right ventricular cardiomyopathy

Continuous telemetry did not reveal arrhythmia or prolonged QTc during hospitalization.

Results of a transthoracic echocardiogram are summarized in Table 1.

The differential diagnosis for syncope was ischemia (given the family history of sudden cardiac death), arrhythmia, RV dysfunction (given the history of CREST syndrome), and arrhythmogenic right ventricular cardiomyopathy (given the findings shown in Table 1).

CREST syndrome causes fibrosis of the myocardium and cardiac conduction system, causing ventricular arrhythmias and sudden cardiac death. The pathologic hallmark of cardiac involvement by CREST syndrome is patchy myocardial fibrosis. CREST syndrome can also present with pulmonary hypertension resulting in RV dysfunction or failure, which is a poor prognostic sign. In addition, myocardial involvement can lead to LV systolic, and more commonly diastolic, dysfunction.

ARVC similarly causes fibrosis and fibro-fatty replacement of the myocardium, leading to RV dilation and myocardial thinning. Most patients also have both LV myocyte loss and fibrosis, which usually involves the lateral and posterior walls of the LV.

Cardiovascular magnetic resonance imaging was performed (Figure 2).

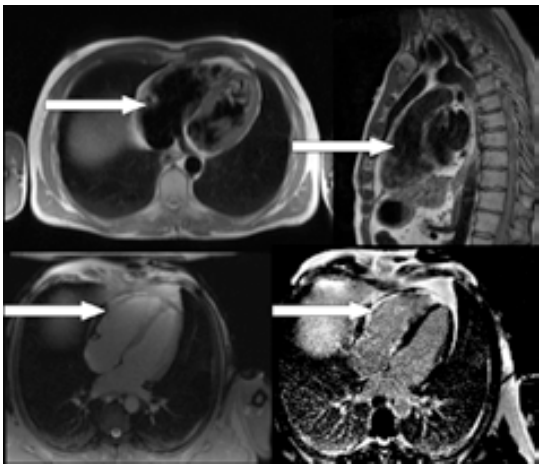

Figure 2: From left to right, top to bottom (arrow indicates RV). Cardiac magnetic resonance image without gadolinium contrast showing thinning of RV free wall and marked RV dilation; cardiac MRI without gadolinium contrast showing RVOT, CMR without gadolinium contrast showing RV wall thinning, CMR revealing late gadolinium enhancement of the RV free wall.

RA & LA	Normal
LV	Mild LV systolic dysfunction
RV body	Dilated
Left Ventricular Structure/Function	
All LV wall segments are hypokinetic, and there is delayed enhancement in the basal-anterior, basal-inferior, and basal-inferolateral walls	
Right Ventricular Structure/Function	
RVEDV (ml)	291
RVESV (ml)	237
RVEF (%)	19
RV Reg. Wall Mot.	Global hypokinesis
Hemodynamic and Functional Data	
LVEF (%)	40
LVESV (ml)	82
LVESI (ml/m2)	40.79
LV Stroke volume (ml)	55
LV Stroke index (ml/m2)	27.36
LVEDV (ml)	137
LVEDI (ml/m2)	68.15
Interpretation	
1. Mild LV septal hypertrophy with normal cavity size. LV systolic function mildly reduced. Calculated LVEF 40%. 2. Global hypokinesis of LV as well as focal posteriobasal wall thickening and akinesis. 3. Thinning of RV free wall and marked dilation of RV cavity. RVEDV indexed to BSA is 144 mL/m^2 (normal range 55-105 mL/m^2). RV systolic function severely reduced. Calculated RVEF 20%. 4. RV severe global hypokinesis. Dyskinesia of the anterior portion of the RVOT. 5. LA and RA normal. 6. Aortic, mitral, tricuspid, and pulmonic valves are pliable. 7. Transmural late gadolinium enhancement of the LV posterior basal wall suggestive of prior infarct, fibrosis, or inflammatory process. 8. Suspected late gadolinium enhancement involving the RV free wall. The RV is severely dilated with severely decreased systolic function. RVEF 20%. There is focal dyskinesia present along the anterior portion of the RVOT. In addition, there is late gadolinium enhancement of the RV free wall consistent with fibrosis and an increased RVEDVi. In the absence of longstanding hypertension, the findings in the RV are worrisome for a RV cardiomyopathy. There is also evidence of LV dysfunction.	

The cardiac MRI results were concerning for ARVC, and showed LV dysfunction with an infarct in the area of the right coronary artery. Subsequent right heart catheterization and coronary angiography revealed:

Site	Baseline values, mm Hg S / D (Mean)
RA	9 / 7 (6)
RV	28 / 9
PA	23 / 13 (17)
PCW	13 /12 (10)
AO	122 / 76 (98)
Cardiac Output (L/min)	5.7
Cardiac Index (L/min/M sq)	2.82
Vascular resistance (dyne sec cm-5)	
Systemic	1291.2
Total Pulmonary	238.6
Pulmonary Arteriolar	98.3
Coronary Angiography	Stenosis (%)
Proximal Circumflex (native)	20
Proximal LAD (native)	30
Proximal RCA (native	20
CONCLUSIONS:	Mild non-obstructive ASCAD; normal pulmonary pressures

Given the infarct substrate and possible ARVC, the patient's syncope was concerning for ventricular tachycardia (VT). The patient had otherwise unexplained syncope and met 2 major diagnostic criteria for ARVC (Figure 3):

Criterion	Patient
By MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *And* 1 of the following: o Ratio of RVEDV to BSA ≥ 110 mL/m2 (male) o *Or* RVEF ≤ 40%	✓ Global RV dyskinesia ✓ Ratio of RVEDV to BSA: 145 mL/m2 ✓ RVEF 19%
Repolarization abnormalities: • Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals > 14 years of age (in the absence of completed right bundle-branch block QRS ≥ 120 ms)	✓ Inverted T waves in V1-V4
Depolarization/conduction abnormalities: • Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)	✓ Subtle epsilon wave in V1-V2

Due to the patient's high risk for sudden cardiac death, a single-chamber implantable cardioverter defibrillator (ICD) was placed for primary prevention. The patient was discharged on a low-dose ACE inhibitor due to decreased ejection fraction, aspirin, and given activity/exercise restrictions. The patient was advised to inform family members of the diagnosis so that they may receive appropriate screening from their respective medical care providers.

Discussion

Arrhythmogenic right ventricular cardiomyopathy (ARVC), known previously as arrhythmogenic right ventricular dysplasia (ARVD), is a type of non-ischemic cardiomyopathy characterized by fibro-fatty replacement of the RV myocardium leading to electrical and structural instability manifesting as ventricular arrhythmias, sudden cardiac death, and heart failure.[1] The incidence is unknown, but the prevalence is estimated to be approximately 1 in 2000 to 1 in 5000.[1] The average age at presentation is 30 years, and it is uncommon before the age of 10.[2-4] Both sexes are affected equally.[5] Some studies have suggested that 30% of cases are familial.[3] Although ARVC is a rare diagnosis in the United States, it may be underrecognized.

ARVC is an inherited disease caused by multiple mutations on genes encoding for desmosomal proteins.[1] It is considered a desmosomal disease, in contrast to hypertrophic cardiomyopathy, a sarcomeric disease, and dilated cardiomyopathy, a cytoskeletal disease.[1] It is hypothesized that mutated desmosomal proteins, in the setting of mechanical stress (such as activity), lead to myocyte detachment from intercalated discs, resulting in myocyte death and fibro-fatty replacement.[1] Loss of cardiac myocytes leads to electrical and structural dysfunction. The cause of RV localization is unknown. Autosomal dominant inheritance is more common, and autosomal recessive inheritance is seen as part of cardiocutaneous syndromes (e.g. Naxos disease, Carvajal syndrome).[6]

Clinical presentation of ARVC can vary, and many patients may be asymptomatic or clinically silent until later in life. Asymptomatic patients may be identified if they have an affected family member. The most common symptoms include palpitations, syncope, atypical chest pain, dyspnea,

and RV failure.[4] Palpitations and syncope may be the clinical manifestation of ventricular arrhythmia.[2, 4]

Ventricular arrhythmias in ARVC range from premature ventricular contractions to sustained ventricular tachycardia (VT).[7] In early disease, the presence of VT is secondary to ARVC and may be a harbinger for sudden cardiac death or heart failure. In late disease, ARVC may lead to heart failure, which itself can produce VT. The ventricular arrhythmias predominantly originate in the RV,but autopsy series have shown histopathologic abnormalities in the LV and bundle of His that may contribute to conduction abnormalities.[5,7] Sudden cardiac death can occur in patients with known ARVC, but death also may be the first presentation of the disease.[1, 3, 7–9]

Ventricular arrhythmias in ARVC can be exercise-induced. In a report from Italy, ARVC accounted for sudden cardiac death in 22% of athletes.[10] In a series in the United States, ARVC accounted for sudden cardiac death in 4% of athletes.[8] Induction of ventricular arrhythmias and sudden cardiac death with exercise is thought to be due to increased stress on the RV as well as abnormal sensitivity to catecholamines.[11]

ARVC can be diagnostically challenging and requires a synthesis of clinical criteria and multiple diagnostic modalities, which alone have limited sensitivity and specificity. Diagnosis is based on the 2010 revised Task Force criteria, which stratifies a diagnosis as definite, borderline, or possible (Figure 3).[12] Initial evaluations in patients with suspected ARVC includes an electrocardiogram and transthoracic echocardiography. Selected additional studies including continuous electrocardiographic monitoring, stress testing, and cardiac MRI (among others), should be performed as clinically warranted. Genetic testing is available and can be diagnostically useful,

	Revised Task Force criteria
I. Global or regional dysfunction and structural alterations*	
Major	**By 2D echo:** • Regional RV akinesia, dyskinesia, or aneurysm • *and* 1 of the following (end diastole): • PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m2) • PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m2) • *or* fractional area change ≤33 percent
	By MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female) • *or* RV ejection fraction ≤40 percent
	By RV angiography: • Regional RV akinesia, dyskinesia, or aneurysm
Minor	**By 2D echo:** • Regional RV akinesia or dyskinesia • *and* 1 of the following (end diastole): • PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2) • PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2) • *or* fractional area change >33 percent to ≤40 percent
	By MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) • *or* RV ejection fraction >40 percent to ≤45 percent
II. Tissue characterization of wall	
Major	• Residual myocytes <60 percent by morphometric analysis (or <50 percent if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor	• Residual myocytes 60 percent to 75 percent by morphometric analysis (or 50 percent to 65 percent if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
Major	• Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)
Minor	• Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 • Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block
IV. Depolarization/conduction abnormalities	
Major	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)
Minor	• Late potentials by SAECG in ≥1 of the following 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG • Filtered QRS duration (fQRS) ≥114 ms • Duration of terminal QRS <40 µV (low-amplitude signal duration) ≥38 ms • Root-mean-square voltage of terminal 40 ms ≤20 µV • Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete right bundle-branch block
V. Arrhythmias	
Major	• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 ventricular extrasystoles per 24 hours (Holter)
VI. Family history	
Major	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria • ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation¶ categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative • ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative
Diagnostic terminology for revised criteria: • Definite diagnosis: 2 Major, OR 1 Major and 2 Minor criteria, OR 4 Minor from different categories • Borderline diagnosis: 1 Major and 1 Minor, OR 3 Minor criteria from different categories • Possible diagnosis: 1 Major, OR 2 Minor criteria from different categories PLAX: parasternal long-axis view; RVOT: RV outflow tract; BSA: body surface area; PSAX: parasternal short-axis view; aVF: augmented voltage unipolar left foot lead; aVL: augmented voltage unipolar left arm lead. * Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria. ¶ A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree. *Modified with permission from: Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force criteria. Circulation 2010; 121:1533.* *Copyright © 2010 Lippincott Williams & Wilkins.* Graphic 58452 Version 12.0	

Figure 3: 2010 revised Task Force criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVC)12

but is not required for patients satisfying the task force criteria for a definite diagnosis.[6] Endomyocardial biopsy is considered the gold standard for diagnosis, since it can help identify the features of ARVC and distinguish it from other conditions (e.g. myocarditis, sarcoidosis, or endomyocardial fibrosis).[12] Limitations of endomyocardial biopsy include low sensitivity (segmental tissue involvement by ARVC creates a sampling challenge) and its invasiveness may pose a risk in a structurally compromised RV.[6]

In addition, family history should be evaluated if ARVC is suspected. Any new diagnosis of ARVC warrants serial clinical evaluation in first-degree relatives (suggested initial electrocardiogram and transthoracic echocardiography, with an annual electrocardiogram thereafter).[13]

There is no known cure for ARVC. Early diagnosis is important for implementation of prevention strategies. The major goal is prevention of sudden cardiac death, and ICD implantation is appropriate for secondary prevention as well as primary prevention in high-risk patients.[13, 14] Despite limited consensus on risk factors identifying those at high risk (aborted sudden cardiac death, sustained VT, syncope, or CHF), the 2006 ACC/AHA/ESC guidelines for the management of ventricular arrhythmias and the prevention of sudden cardiac death, as well as the 2012 ACCF/AHA/HRS guidelines on device-based therapy for cardiac rhythm abnormalities, both addressed the use of an ICD in patients with ARVC.[13, 14] Antiarrhythmic agents such as sotalol or amiodarone may be used as an adjunct to ICD or for those who are not candidates for ICD. Radiofrequency ablation is rarely effective due to the segmental and progressive nature of the disease.[7] Other prevention strategies include exercise/activity restriction.[3, 15] Based on the association of exercise and disease development in ARVC, the use of beta-blockers to attenuate sympathetic stimulation may be beneficial.[16] Patients with heart failure should receive standard therapy for that disorder.

ARVC is a progressive disease, with impending risk of developing ventricular arrhythmias, sudden cardiac death, and heart failure. Prognosis varies for those who are initially asymptomatic and identified by familial disease versus those identified with VT. A 2013 meta-analysis of 610 patients with ICDs for either primary or secondary prevention reported the annualized rated of cardiac death, non-cardiac death, and heart transplantation were 0.9%, 0.8%, and 0.9%, respectively.[17]

In one series, the presence of right or left ventricular dysfunction was the strongest independent predictor of cardiovascular death.[4] In a series of 100 patients with ARVC in the United States, 34 patients died either at presentation (n=23: 21 sudden cardiac death, 2 non-cardiac deaths) or during follow-up (n=11: 10 sudden cardiac death, 1 of biventricular heart failure).[2] On Kaplan-Meier analysis, the median survival in this series was 60 years.[2] In another series of 130 patients with ARVC in France, 24 patients died, of which 21 were cardiovascular deaths, and of those 1/3 were due to sudden cardiac death and 2/3 were due to heart failure.[4] However, once diagnosed and treated with an ICD, mortality is low.[2]

Conclusion

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a non-ischemic cardiomyopathy predominantly affecting the right ventricle (RV) that leads to ventricular arrhythmia, sudden cardiac death, and heart failure. In the absence of ischemia and pulmonary hypertension, ARVC should be suspected in patients with RV cardiomyopathy and/or those with strong family history.

Both CREST syndrome and ARVC can present with patchy fibrosis of the myocardium involving both the RV and LV, arrhythmia, syncope, sudden cardiac death, and heart failure. Ultimately, the patient's extensive work-up for syncope identified a new diagnosis of ARVC and a family history that suggested concern for extensive ischemic heart disease.

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