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Arrhythmogenic right ventricular cardiomyopathy/dysplasia in Saudi Arabia: a single-center experience with long-term follow-up

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BACKGROUND AND OBJECTIVES: Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a rare genetic disorder that primarily involves the right ventricle (RV). It is characterized by progressive replacement of RV myocardium by fibrofatty tissues. It commonly presents with ventricular tachycardia (VT) of RV origin and may result in RV failure. The aim of this study is to evaluate the clinical characteristics of adult patients with ARVC/D treated at the Heart Centre, King Faisal Specialist Hospital and Research Centre (KFSH&RC), Riyadh, Saudi Arabia.

DESIGN AND SETTINGS: This is a retrospective study of patients with ARVC/D diagnosed and treated at the KFSH&RC Heart Centre in Riyadh.

PATIENTS AND METHODS: Twenty-two cases with ARVC/D with regular follow-up at our Heart Centre from January 2007 to May 2010 were included in this study. The diagnosis of ARVC/D was made according to the revised International Task Force Criteria. The clinical data were collected from patients' charts and electronic medical records.

RESULTS: The majority of patients were males (18; 82%). The diagnosis of ARVC/D was definite in 18 patients (82%), borderline in 2 (9%), and possible in 2 (9%). The mean age at diagnosis was 33.3 years. The follow-up period ranged from 29 to 132 months, with a mean follow-up period of 84 months. Ten patients presented with sustained VT, and 3 were survivors of cardiac arrest. Electrocardiogram abnormalities were present in 16/22 patients (72.7%). Echocardiographic changes meeting major diagnostic criteria were seen in 16 patients (76%). Cardiac magnetic resonance imaging was performed in 11 patients, and showed changes compatible with major diagnostic criteria in 7 patients (64%). Implantable cardioverter defibrillators (ICDs) were implanted in 17 patients; 8 had appropriate ICD shocks and 5 had inappropriate ICD shocks. Antitachycardia pacing was effective in terminating most of the VT/ventricular fibrillation episodes.

CONCLUSION: ARVC/D is a rare but increasingly recognized heart muscle disease seen in Saudi Arabia and other parts of the world. It is associated with a highly nonspecific presentation. VT of RV origin is a common presentation for this disease. Antiarrhythmic medications and ICD implantation are the main management options.

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a rare genetic disorder that primarily involves the right ventricle (RV). It is characterized by progressive replacement of the RV myocardium by fatty and/or fibrofatty tissue. The structural changes in the ventricular myocardium form a substrate for arrhythmia and may result in RV failure, progressing to congestive heart failure at a later stage.

ARVC/D was first described by Frank et al in 1978,[1] and the first clinical profile of the disease was published in 1982.[2] ARVC/D was recognized as a distinct cardiomyopathy 18 years later.[3,4] Our understanding of this disease was initially drawn from multiple, small, highly

selected case series;[5,6] however, a prospective study has recently been published.[7]

The most common clinical presentation of ARVC/D is ventricular arrhythmia, arising predominantly from the RV. These arrhythmias range from isolated premature ventricular beats to sustained ventricular tachycardia (VT) or ventricular fibrillation that may lead to sudden death. The most common presenting symptoms of the disease are palpitations, chest discomfort, near syncope, or syncope.

A genetic background has been demonstrated in 30%-50% of ARVC/D cases.[8] The disease is typically inherited as an autosomal dominant trait with variable penetration and incomplete expression. Most of the genes identified code desmosome family proteins, which are involved with cell-to-cell adhesion. These mutations involve predominantly plakophilin desmosomes.[9,10] Recently, plakoglobin has been identified as the first gene responsible for the autosomal recessive variant of the disease, the so-called "Naxos disease."[11,12]

The diagnosis of ARVC/D is often difficult because there is no single investigation that can be used to establish or exclude the diagnosis. However, the results of a history, physical examination, and a number of specific cardiac tests, including electrocardiogram (ECG), echocardiogram, cardiac magnetic resonance imaging (CMRI), and RV, can be used to establish the diagnosis.

The original International Task Force Criteria for the clinical diagnosis of ARVC/D were published in 1994 and were based on structural, histological, ECG, arrhythmic, and familial features of the disease.[13] Abnormalities are subdivided into major and minor categories according to the specificity of their association with ARVC/D. The diagnosis of ARVC/D is fulfilled by the presence of 2 major criteria or 1 major and 2 minor criteria, or 4 minor criteria from different groups.

The Task Force Criteria were based on studying symptomatic index cases and sudden cardiac death victims. These cases represent the overt or severe end of the disease spectrum. Consequently, the 1994 criteria were highly specific, but they lacked sensitivity for early and familial disease.[14] The 2010 updated Task Force Guidelines incorporated advances in our understanding, particularly in the genetics of ARVC/D and the technology, to improve diagnostic sensitivity with maintaining diagnostic specificity. They include quantitative, structural, electrocardiographic, and histological parameters to aid diagnosis (**Table 1**).[15]

To our knowledge, there has been no study examining the clinical characteristics in ARVC/D patients in Saudi Arabia, apart from a single case report.[16] Therefore, the purpose of this study was to present the clinical characteristics and long-term follow-up of ARVC/D patients at the Heart Centre, King Faisal Specialist Hospital and Research Centre (KFSH&RC) a tertiary care center in Riyadh, Saudi Arabia.

The main aim of this study was to evaluate the clinical characteristics of adult patients with ARVC/D treated at our Heart Centre (**Appendix 1**).

PATIENTS AND METHODS

This study was a retrospective analysis of the medical charts and electronic medical records of adult patients (age: >18 years) with a possible, borderline, or definite diagnosis of ARVC/D, based on the revised ARVC/D Task Force diagnostic criteria,[15] who were on regular follow-up at our Heart Centre from January 2007 to May 2010. This study was approved by the KFSH&RC Research Ethics Committee.

Diagnosis of ARVC/D
The diagnosis of ARVC/D was based on the criteria outlined in the revised Task Force Criteria. These were:
* definite ARVC/D with 2 major or 1 major and 2 minor criteria or 4 minor criteria from different categories;
* borderline ARVC/D with 1 major and 1 minor or 3 minor criteria from different categories; and
* possible ARVC/D with 1 major or 2 minor criteria from different categories.

The following data were recorded:
* detailed description of the presenting complaints, including dizziness, palpitations, presyncope, syncope, chest pain, limitation of exercise tolerance, and a family history;
* ECG at presentation and follow-up, and any detected repolarization and depolarization abnormalities;
* a full transthoracic echocardiography, as outlined in the revised ARVC/D Task Force Criteria,[16] which we used to look for right ventricular segmental or regional dilatation, aneurysms, or morphological abnormalities;
* exercise test and 24-hour Holter monitoring in selected cases;
* CMRI to assess RV and left ventricular (LV) function, segmental/regional dilatation, and end diastolic volumes in 11 cases; and
* invasive diagnostic investigations, such as coronary angiography, endomyocardial biopsy, and electrophysiology studies, were performed depending on clinical indications.

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Table 1. The Revised Task Force Criteria for ARVC/D diagnosis.

	Major criteria	Minor criteria

I. Global or regional dysfunction and structural alterations	**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%
	
	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%
	
	By RV angiography:
	- Regional RV akinesia, dyskinesia, or aneurysm
		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/m²)
		  • PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m²)
		  • or fractional area change >33% to ≤40%
		
		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/m² (male) or ≥90 to <100 mL/m² (female)
		  • or RV ejection fraction >40% to ≤45%

II. Tissue characterization of wall	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	Residual myocytes 60%-75% by morphometric analysis (or 50%-65% 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	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)	- 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	Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1-V3)	- Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG - fQRS duration ≥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	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)	- 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 h (Holter)
VI. Family History	- 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	- 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

Notes: Diagnostic terminology: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories. *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; eg, in TMEM43, DSP, PKP2, DSG2, DSC2, and JUP. Adapted from www.ARVD.com.

Abbreviations: ARVC/D: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; 2D: 2-dimensional; echo: echocardiography; RV: right ventricle; PLAX: parasternal long-axis view; RVOT: right ventricular outflow tract; BSA: body surface area; PSAX: parasternal short-axis view; SAECG: signal-averaged electrocardiography; ECG: electrocardiogram; fQRS: filtered QRS aVF: augmented voltage unipolar left foot lead; aVL: augmented voltage unipolar left arm lead.

Implantable Cardioverter Defibrillators
As ARVC/D is one of the causes of sudden cardiac death in young people,[17] implantation of an implantable cardioverter defibrillator (ICD) is indicated in ARVC/D patients who survive cardiac arrest, have VT, or who have other high-risk features like unexplained syncope. Patients requiring ICD implantation had a transvenous system implanted.

RESULTS

This study is a presentation of 22 clinical cases with definite, borderline, or possible ARVC/D diagnosed on the basis of the revised ARVC/D Task Force Criteria.[15] The majority of patients were male (18; 82%). Utilizing the revised Task Force Criteria,[15] 18 patients (82%) had definite ARVC/D, 2 patients (9%) had borderline ARVC/D, and 2 patients (9%) had possible ARVC/D. The patients' ages ranged from 18-62 years, with a mean age of 38.6 years. The age at diagnosis ranged from 17-52 years, with a mean age of 33.3 years. The follow-up period ranged from 29-132 months, with a mean follow-up period of 84 months.

Eighteen patients experienced palpitations of variable duration prior to presentation. Sustained VT was a common presenting symptom; 10 patients presented with documented sustained VT, and 3 of these patients had cardiac arrest requiring cardiopulmonary resuscitation and direct current shocks at their first presentation. The other presenting symptoms included shortness of breath in 8 patients, syncope and presyncope in 7 patients, chest pain in 4 patients, and dizziness in 3 patients.

A family history of ARVC/D was present in 1 family, with 4 members affected. Seven patients had a history of sudden death in at least 1 first-degree relative under the age of 35 years. The clinical characteristics of the patients are summarized in **Table 2**.

ECG Abnormalities
Electrocardiographic abnormalities presented in 16/22 patients (72.7%) (**Figure 1**). Repolarization abnormalities were present in 15 patients; depolarization abnormalities (epsilon wave) were seen in 5 patients (22.7%), and wide QRS complex in V1–V3 (>110 ms) in 2 patients. Twenty-four-hour Holter monitoring demonstrated frequent premature ventricular contractions and nonsustained VT in 6 patients. Signal-averaged ECG was not performed in our patients (**Table 3**).

Echocardiogram
Echocardiography was performed in all patients. Typical ARVC/D changes meeting major diagnostic criteria were seen in 16 patients (76%) (**Figure 2**). Milder echocardiographic changes meeting minor diagnostic criteria were seen in 2 patients (10%).

Cardiac MRI
CMRI was performed in 11 patients, and showed changes compatible with major diagnostic criteria in 7 patients (64%) and changes compatible with minor criteria in 3 patients (27%) (**Figure 3**).

Invasive Diagnostic Workup
Right ventriculography was performed in only 1 patient and showed reduced RV function with RV dilatation. Also, RV endomyocardial biopsy was performed from the interventricular septum in 1 patient; it was reported as normal (**Table 4**). Electrophysiology studies were performed in 6 patients. All had inducible VT from RV origin, and ablation of VT was performed in 3 patients. Cardiac catheterization was performed in 3 patients, and all had normal coronaries.

Genetic Testing
Genetic testing was performed in 13 patients; 7 were positive, with 5 mutations in the *PKP2* gene (common in ARVC/D patients),1 mutation in the *DSP* gene, and 1 mutation in the *DSC2* gene.

Medical Management
Patients with a significant reduction in RV or LV systolic function were treated with beta-blockers and angiotensin-converting enzyme inhibitors. Eighteen patients (81.8%) were on antiarrhythmic medications, with sotalol (9 patients) and amiodarone (4 patients) being the most commonly used antiarrhythmic medications.

Radiofrequency Catheter Ablation
In our study, 6 patients underwent an electrophysiology study (EPS); 2 were diagnosed at other cardiac centers withidiopathic RV outflow tract VT and had undergone attempts to ablate VT. Once the diagnosis of ARVC/D was established, they underwent ICD implantation. Two patients had EPS in another institution; we do not have the details of this study. One patient had EPS and ablation for recurrent ICD shocks, and 1 patient had EPS to assess for VT inducibility, which was negative.

ICD Therapy
ICDs were implanted in 17 patients, and 5 patients refused ICD implantation. Eight patients had appropriate ICD shocks and 5 patients had inappropriate ICD

Table 2. Clinical characteristics of the patients.

	Gender	Age at diagnosis	Presentation	Family history	Follow-up (mo)
1	M	52	VT Dizziness/Syncope Palpitation SOB	–	132
2	M	30	Palpitation VT SOB Cardiac arrest	3 Brothers with ARVC/D	119
3	M	25	Presyncope Palpitation VT (nonsustained)	3 Brothers with ARVC/D	63
4	M	17	Palpitation VT	3 Brothers with ARVC/D	117
5	M	16	Palpitation VT (nonsustained) Syncope	3 Brothers with ARVC/D	111
6	F	39	Palpitation	Sudden death in 2 brothers at age <35 yr	118
7	M	50	Palpitation VT	–	110
8	M	41	VT Syncope	–	98
9	M	42	Palpitation VT	–	61
10	M	18	Recurrent VT Palpitation	–	66
11	M	30	Palpitation SOB Chest pain Syncope (vasovagal)	Sudden death of 1 brother at age 18 yr	48
12	F	44	Palpitation SOB	Sudden death of father (age 30) and 1 brother (age 22)	32
13	F	25	Palpitation dizziness	Sudden death in 1 sister at age 22 years	29
14	M	17	Palpitation Dizziness/Presyncope	–	31
15	M	24	Syncope palpitation	–	29
16	F	44	Palpitation PVCs	–	30
17	M	49	VT	Sudden death of 2 uncles <35 yr of age	34
18	M	37	Chest pain Palpitation VT	–	183
19	M	40	Palpitation Chest pain VT Cardiac arrest	–	81
20	M	49	Palpitation VT	–	103
21	M	33	SOB VT Chest pain	Sudden death in 1 brother who died at age <35 yr	63
22	M	37	Palpitation	Sudden death in 2 brothers at age 29 and 31 yr	106

Abbreviations: M: Male; VT: ventricular tachycardia; SOB: shortness of breath; ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia; F: female; PVC: premature ventricular contraction.
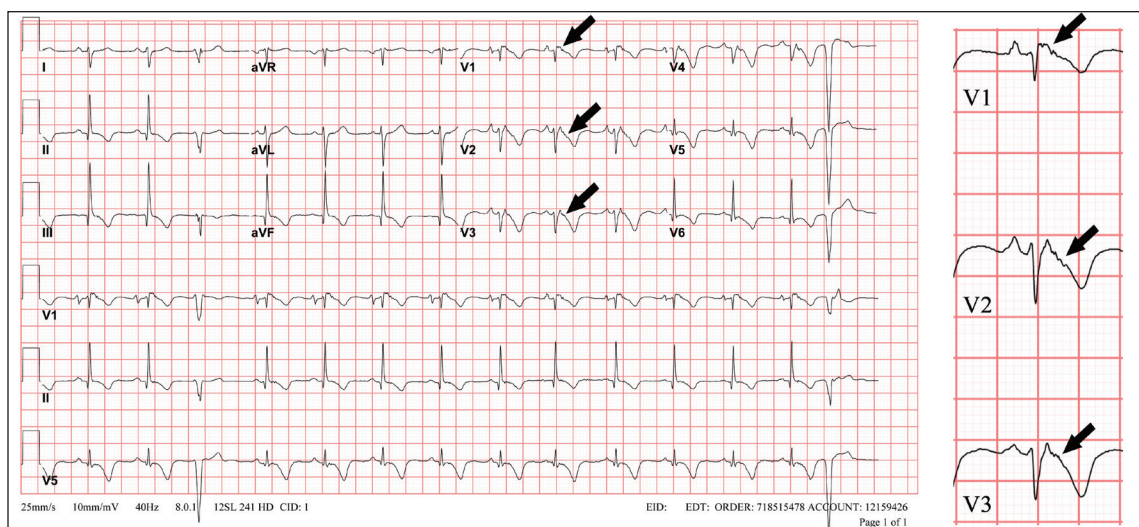
Figure 1. A 12-lead ECG of a patient with ARVC/D shows sinus rhythm 60 beats per minute, T wave inversion in V1 to V6 and the presence of Epsilon wave in V1 to V3 (black arrows) (low amplitude potentials at the end of QRS complex) and PVCs of LBBB-like morphology and superior axis. Magnification of V1 to V3 shows the Epsilon wave (black arrow).

Table 3. ECG characteristics.

Patient	Epsilon	TWI V1–V3	TWI V1–V2 or V4–V6	RBBB+TWI V1–V4	QRS width V1–V3	Terminal QRS> 110 ms
1	+	+	–	–	–	+
2	–	+	–	–	–	+
3	–	+	–	–	–	–
4	–	+	–	–	–	–
5	–	+	–	–	–	–
6			–	–	–	–
7	+	+	–	–	–	–
8	+	+	–	–	–	–
9	–	+	–	–	–	–
10	–	+	–	–	–	–
11	–		–	–	–	–
12	+	+	–	–	–	–
13	–	+	–	–	–	–
14	–		–	–	–	–
15	–		–	–	–	–
16	–		–	–	–	–
17	–		–	–	–	–
18	–	+	–	–	–	–
19	–	+	–	–	–	–
20	–	+	–	–	–	–
21	+		–	+	+	–
22	–	–	–	–	+	–

Notes: +, Present; –, absent. Abbreviations: ECG: Electrocardiogram; TWI: T-wave inversion; RBBB: right bundle-branch block.

shocks during follow-up. Six patients had electrical storm with multiple ICD discharges, which improved with the correction of electrolyte abnormalities and initiating or changing antiarrhythmic medications.

DISCUSSION

All of our patients were diagnosed on the basis of non-invasive diagnostic tests without a need for invasive testing, such as endomyocardial biopsy.

Most of our patients were males (18/22; 82%), which is consistent with previous studies that showed a higher prevalence of ARVC/D in men.[18,19] However, the male-to-female ratio was 4.5:1, which is higher than the previously reported ratio of 1.6 to 2.7:1. It is possible that we have fewer female patients due to referral bias and less acceptance of ICD in our female patients.

We included only adult patients, and the age of presentation in our patients was 17-52 years (mean: 33.3 years). The incidence of ARVC/D is highest between 5 and 40 years.[20]

Most of our patients presented with palpitations; VT was also a common presenting event. Previous studies have shown that individuals with ARVC/D present with palpitations (67%), syncope (32%), atypical chest pain (27%), or RV failure (6%) are asymptomatic (6%).[21] Four of our patients were initially diagnosed with idiopathic VT, but follow-up ECGs and cardiac imaging showed changes consistent with ARVC/D. Those patients likely had electrical manifestations of the disease before having obvious structural changes. Two of these patients were diagnosed with idiopathic VT of RV outflow tract origin and underwent multiple EPS and ablations in other institutions with no success. The diagnostic workup of these 2 patients showed that they had a definite diagnosis of ARVC/D.

ECG is an important diagnostic tool in ARVC/D. ECG abnormalities are present in up to 90% of ARVC/D patients.[21,22] The most common abnormality consists of T-wave inversion, often associated with a slight ST-segment elevation <0.1 mV in precordial leads V1 to V3 exploring the RV. These repolarization changes were noted in 15 of our patients (68%). Relatively, the most ARVC/D-specific ECG diagnostic marker is the presence of epsilon waves (postexcitation potentials of small amplitude that occur at the end of QRS complex) found in up to 30% of cases of ARVC/D and localized prolongation of the QRS complex in V1 to V3 to more than 110 ms (found in up to 60% of cases of ARVC/D).[19,21-23]

The epsilon waves were observed in 5 of the cases analyzed (22.7%), but QRS complex duration of 110 ms or more in V1 to V3 was present in 2 cases only.
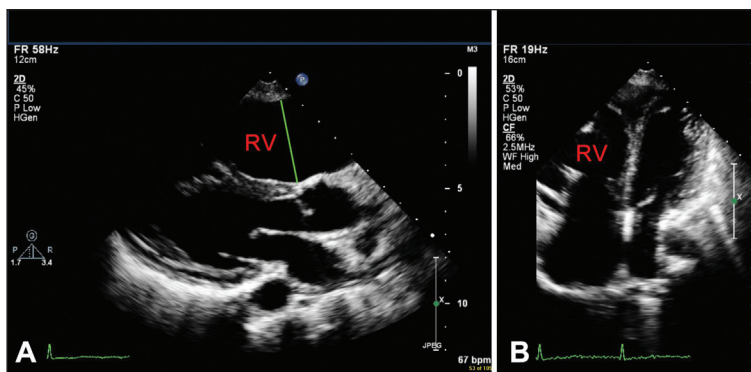

Figure 2. Parasternal long axis (A) and apical 4-chamber (B) echocardiographic views showing RV dilatation in a patient with ARVC/D. RV: right ventricle.
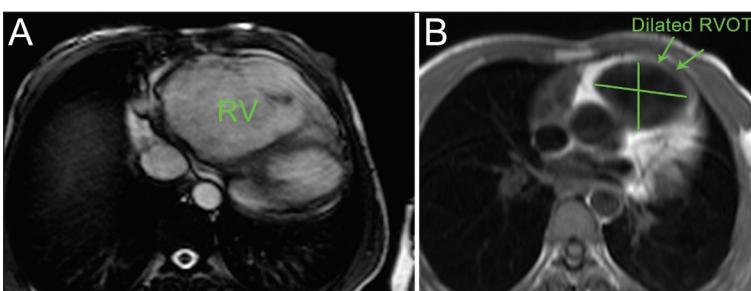

Figure 2. (A) Axial cine-SSFP (steady-state free precession) MRI showing significant RV dilatation and (B) black-blood-prepared HASTE (half-Fourier acquired single-shot turbo-spin echo) axial slice MRI at the level of right ventricular outflow tract (RVOT) showing RVOT dilatation. MRI: Magnetic resonance imaging; RV: right ventricle.

Another very helpful and useful method of diagnosing ARVC/D is echocardiography. This technique, which is noninvasive, widely available, low in cost, and easy to perform and interpret, has played a crucial role in imaging structural and functional abnormalities of the RV. Right ventricular function should be measured at several points, including the inflow and outflow tracts because of the focal nature of the disease.[24-26]

The echocardiographic findings most suggestive of ARVC/D include dilatation of the RV with localized aneurysms and dyskinesis in the inferior basal region.[24-26] Right ventricular end diastolic and end systolic diameters are very useful echocardiographic parameters in establishing the diagnosis of ARVC/D, as well as the ratio of the RV to LV end diastolic diameters (a ratio >0.5 for the RV/LV end diastolic diameter have a sensitivity of 86% and a specificity of 93% for the diagnosis of ARVC/D).[24-26] There are numerous reports of the use of echocardiography to aid in the diagnosis of ARVC/D. These studies have found that the presence of right ventricular dysfunction by 2-dimensional echocardiography has a high specificity and predictive value for ARVC/D.[24-26] The development of new echocardio-

Table 4. ARVC/D diagnoses.

Patient	ECG repolarization	ECG depolarization	Arrhythmia	ECHO	MRI	Endomyocardial biopsy	Familial history	Diagnosis
1	++	++	+	++	NA	NA	–	D
2	++	–	+	++	NA	NA	++	D
3	++	–	+		+	NA	++	D
4	++	–	+	++	NA	NA	++	D
5	++	–	+	++	NA	NA	++	D
6	–	–	+	+	–	NA	+	B
7	++	++	+	++	NA	NA	–	D
8	++	++	+	++	+	NA	–	D
9	++	–	+	++	NA	NA	–	D
10	++	–	+	++	++	NA	–	D
11	–	–	+	+	+	Negative	+	B
12	++	++	+	++	++	NA	+	D
13	++	–	+	++	++	NA	+	D
14	–	–	+	++	++	NA	+	D
15	–	–	–	+	+	NA	–	P
16	–	–	+	++	++	NA	+	D
17	–	–	+		+	NA	–	P
18	++	–	+	+	NA	NA	–	D
19	++	–	++	+	NA	NA	–	D
20	++	–		++	NA	NA	–	D
21	++	++	++	++	++	NA	+	D
22	–	–	+	–	+	NA	+	B

Notes: –, Criterion not present; +, minor criterion; ++, major criterion. Abbreviations: ARVC/D: arrhythmogenic right ventricular cardiomyopathy/dysplasia; ECG: electrocardiogram; ECHO: echocardiogram; MRI: magnetic resonance imaging; NA: not applicable; D: definite diagnosis of ARVC/D; B: borderline diagnosis of ARVC/D; P: possible diagnosis of ARVC/D.

graphic techniques such as 3-dimensional harmonic imaging and tissue Doppler may help in minimizing the number of false-negative echocardiographic results.

In our study, echocardiographic abnormalities fulfilling major diagnostic criteria were seen in 16 patients and minor diagnostic criteria in 2 patients. LV involvement with a left ventricular ejection fraction less than 40% was noted in 3 patients.

CMRI has recently been added to the techniques used to diagnose ARVC/D. CMRI has the advantage of assessing the RV (and LV) function, size, global or regional wall motion abnormalities, and quantification of myocardial wall thinning and hypertrophy.

Quantitative analysis showed that RV end diastolic diameter and outflow tract area were significantly higher and RV ejection fractions lower in ARVC/D pa-

tients when compared to controls.[27-29] Although CMRI is a potentially useful test because it can distinguish fat from muscle, the sensitivity and specificity of CMRI detection of RV intramyocardial fat in the diagnosis of ARVC/D is variable, ranging from 22% to 100%.[27-32] Identifying fat can be challenging because of the thin RV wall; therefore, it is difficult to distinguish pathologic adipose infiltration from adjacent epicardial fat.

Our patients presented in the late 1990s and early 2000s with documented VT, or following resuscitation after cardiac arrest, they underwent cardiac evaluation with echocardiography and ICD implantation for the secondary prevention of sudden cardiac death; therefore, CMRI was not performed. Thirteen patients had CMRI; 60% of them (7 patients) had CMRI changes compatible with major diagnostic criteria, and 27% (3

patients) had changes compatible with minor criteria.

Various drugs have been investigated to suppress the possible life-threatening arrhythmias of ARVC/D, including beta-blockers, sotalol, and amiodarone.[33,34] Sotalol may be the most efficacious drug, with an overall efficiency rate of 68% and 83% in treating both inducible and noninducible VT, respectively, in ARVC/D. However, due to the progressive nature of the disease, arrhythmias may recur despite the initial success of drug therapy. Evidence from a small number of patients suggests that amiodarone has superior efficacy in preventing VT.[34]

Radiofrequency catheter ablation (RFA) has been used in managing patients with ARVC/D and recurrent VT.[35-39] The reported success of ablation in ARVC/D varies, with acute success ranging from 41% to 88% and chronic success (>12 months follow-up) ranging from 7% to 88% free of any VT, with the assumption that recurrence was due to progression of the disease. Radiofrequency ablation therapy cannot be recommended as an alternative to ICD implantation at the current time. Radiofrequency ablation should be tried in patients with frequent VT or ICD shocks despite optimal antiarrhythmic therapy (Class IIa recommendation). In a study with 24 patients (age: 36±9 years; 11 male) enrolled in the Johns Hopkins ARVD registry who underwent 1 or more RFA procedures for the treatment of VT, with a follow-up period of 32±36 months (range,: day to 12 years), the cumulative VT recurrence-free survival was 75%, 50%, and 25% after 1.5 months, 5 months, and 14 months, respectively.[20]

The implantation of an ICD device can effectively terminate life-threatening arrhythmias in patients with ARVC/D and it is considered a standard therapy. Accepted indications for ICD therapy are the prevention of sudden cardiac death in ARVC/D patients with documented sustained VT or ventricular fibrillation (Class I recommendation) and patients with high-risk features such as extensive disease, a positive family history, or undiagnosed syncope (Class IIa recommendation).[36] The experience with ICD therapy in patients with ARVC/D has been reported in several series. Appropriate ICD therapy occurs in 33% to 78% of patients, and inappropriate ICD shock occurs in 10% to 44% of ARVC/D patients.[20] Antitachycardia pacing (ATP) is particularly effective at terminating VTs in ARVC/D patients most of the time.

ICDs were implanted in 17 of our patients; 5 patients refused ICD implantation. Eight patients had appropriate ICD shocks and 5 patients had inappropriate ICD shocks during follow-up. Six patients had an electrical storm with multiple ICD discharges, which improved with the correction of electrolyte abnormalities and initiating or changing antiarrhythmic medications. ATP was effective at terminating most of the VT episodes (67.9%); appropriate ICD shocks were delivered in about one-third of these episodes (28.7%), and inappropriate ICD therapy was delivered in 3.4% of the episodes. The causes of inappropriate shocks included atrial fibrillation, supraventricular tachycardia, sinus tachycardia, and electromagnetic interference.

In conclusion, ARVC/D is a rare but increasingly recognized heart muscle disease seen in Saudi Arabia and in other parts of the world. It is associated with a highly nonspecific presentation. VT of RV origin is a common presentation for this disease. Antiarrhythmic medications and ICD implantation are the main management options. VT of right ventricular origin can be the first presentation and may precede overt structural cardiac changes. Patients with established ARVC/D have a high incidence of appropriate ICD therapy, including ATP therapy and shocks. In all of our cases, an accurate diagnosis of ARVC/D was made on the basis of ECG abnormalities, echocardiography, and CMRI, fulfilling the major and/or minor revised diagnostic criteria without the need for invasive procedures.

REFERENCES

1. Frank R, Fontaine G, Vedel J, et al. [Electrocardiology of 4 cases of right ventricular dysplasia inducing arrhythmia]. Arch Mal Coeur Vaiss. 1978;71(9):963–972. French.

2. Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation. 1982;65(2):384–398.

3. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of cardiomyopathies. Circulation. 1996;93(5):841–842.

4. Maron BJ, Towbin JA, Thiene G, et al; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807–1816.

5. Lemery R, Brugada P, Janssen J, Cheriex E, Dugernier T, Wellens HJ. Nonischemic sustained ventricular tachycardia: clinical outcome in 12 patients with arrhythmogenic right ventricular dysplasia. J Am Coll Cardiol. 1989;14(1):96–105.

6. Ellinor PT, MacRae CA, Thierfelder L. Arrhythmogenic right ventricular cardiomyopathy. Heart Fail Clin 2010;6(2):161–177.

7. Marcus FI, Zareba W, Calkins H, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia clinical presentation and diagnostic evaluation: results from the North American Multidisciplinary Study. Heart Rhythm. 2009;6(7):984–992.

8. Hamid MS, Norman M, Quraishi A, et al. Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. J Am Coll Cardiol. 2002;40(8):1445–1450.

9. van Tintelen JP, Entius MM, Bhuiyan ZA, et al. Plakophilin-2 mutations are the major determinant of familial arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circulation. 2006;113(13):1650–1658.

10. Wlodarska EK, Konka M, Kepski R, et al. Familial form of arrhythmogenic right ventricular cardiomyopathy. Kardiol Pol. 2004;60(1):1–14.

11. Antoniades L, Tsatsopoulou A, Anastasakis A, et al. Arrhythmogenic right ventricular cardiomyopathy caused by deletions in plakophilin-2 and plakoglobin (Naxos disease) in families from Greece and Cyprus: genotype-phenotype relations, diagnostic features and prognosis. Eur Heart J. 2006;27(18):2208–2216.

12. McKoy G, Protonotarios N, Crosby A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet. 2000;355(9221):2119–2124.

13. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J. 1994;71(3):215–218.

14. Marcus FI, Sherrill D. Strengths and weaknesses of the task force criteria: proposed modifications in arrhythmogenic right ventricular cardiomyopathy/dysplasia. In: Marcus FI, Nava A, Thiene G, Eds. Arrhythmogenic Right Ventricular Cardiomyopathy Dysplasia. Milan, Italy: Springer Verlag, 2007:97–104.

15. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J. 2010;31(7):806–814.

16. Wong AR, AbdurRazak N, Al-Hadlaq SM, Al-Jarallah AS. Arrhythmogenic right ventricular cardiomyopathy in an 11-year-old girl and typical echocardiographic features. Pediatr Cardiol. 2008;29(2):427–430.

17. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med. 1988;318(3):129–133.

18. Bauce B, Frigo G, Marcus FI, et al. Comparison of clinical features of arrhythmogenic right ventricular cardiomyopathy in men versus women. Am J Cardiol. 2008;102(9):1252–1257.

19. Prakasa KR, Calkins H. Arrhythmogenic right ventricular dysplasia/cardiomyopathy. Curr Treat Options Cardiovasc Med. 2005;7(6):467–475.

20. Herren T, Gerber PA, Duru F. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: a not so rare "disease of the desmosome" with multiple clinical presentations. Clin Res Cardiol. 2009;98(3):141–158.

21. Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation. 2004;110(12):1527–1534.

22. Gemayel C, Pelliccia A, Thompson PD. Arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol. 2001;38(7):1773–1781.

23. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? Circulation. 1996;94(5):983–991.

24. Lindstrom L, Wilkenshoff U, Larsson H, Wranne B. Echocardiographic assessment of arrhythmogenic right ventricular cardiomyopathy. Heart. 2001;86(1):31–38.

25. Marcus FI, Fontaine G. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: a review. Pacing Clin Electrophysiol. 1995;18(6):1298–1314.

26. Yoerger DM, Marcus F, Sherrill D, et al; Multidisciplinary Study of Right Ventricular Dysplasia Investigators. Echocardiographic findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia: new insights from the multidisciplinary study of right ventricular dysplasia. J Am Coll Cardiol. 2005;45(6):860–865.

27. Tandri H, Calkins H, Nasir K, et al. Magnetic resonance imaging findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia. J Cardiovasc Electrophysiol. 2003;14(5):476–482.

28. American College of Cardiology Foundation Task Force on Expert Consensus Documents, Hundley WG, Bluemke DA, Finn JP, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol. 2010;55(23):2614–2662.

29. Tandri H, Friedrich MG, Calkins H, Bluemke DA. MRI of arrhythmogenic right ventricular cardiomyopathy/dysplasia. J Cardiovasc Magn Reson. 2004;6(2):557–563.

30. Van der Wall EE, Kayser HW, Bootsma MM, de Roos A, Schalij MJ. Arrhythmogenic right ventricular dysplasia: MRI findings. Herz. 2000;25(4):356–364.

31. Jain A, Tandri H, Calkins H, Bluemke DA. Role of cardiovascular magnetic resonance imaging in arrhythmogenic right ventricular dysplasia. J Cardiovasc Magn Reson. 2008;10:32.

32. Tandri H, Castillo E, Ferrari VA, et al. Magnetic resonance imaging of arrhythmogenic right ventricular dysplasia: sensitivity, specificity, and observer variability of fat detection versus functional analysis of the right ventricle. J Am Coll Cardiol. 2006;48(11):2277–2284.

33. Wichter T, Borggrefe M, Haverkamp W, Chen X, Breithardt G. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. Results in patients with inducible and noninducible ventricular tachycardia. Circulation. 1992;86(1):29–37.

34. Marcus GM, Glidden DV, Polonsky B, et al; Multidisciplinary Study of Right Ventricular Dysplasia Investigators. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. J Am Coll Cardiol. 2009;54(7):609–615.

35. Aliot EM, Stevenson WG, Almendral-Garrote JM, et al; European Heart Rhythm Association (EHRA); Registered Branch of the European Society of Cardiology (ESC); Heart Rhythm Society (HRS); American College of Cardiology (ACC); American Heart Association (AHA). EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart Rhythm. 2009;6(6):886–933.

36. Zipes DP, Camm AJ, Borggrefe M, et al; American College of Cardiology/American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114(10):e385–e484.

37. Kuck KH, Ernst S, Dorwarth U, Hoffmann E, Pitschner H, Tebbenjohanns J, Kottkamp H. [Guidelines for catheter ablation]. Clin Res Cardiol 2007;96(11):833–849. German.

38. Verma A, Kilicaslan F, Schweikert RA, et al. Short- and long-term success of substrate-based mapping and ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia. Circulation. 2005;111(24):3209–3216.

39. Dalal D, Jain R, Tandri H, et al. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol. 2007;50(5):432–440.

original article

Appendix 1. STROBE Statement - Checklist of Items that should be Included in Reports of Observational Studies.

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Cohort study - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study - For matched studies, give matching criteria and number of exposed and unexposed Case-control study - For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8[a]	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) Cohort study: If applicable, explain how loss to follow-up was addressed Case-control study - If applicable, explain how matching of cases and controls was addressed Cross-sectional study - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram

Descriptive data	14[a]	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Cohort study - Summarise follow-up time (eg, average and total amount)
Outcome data	15[a]	Cohort study - Report numbers of outcome events or summary measures over time Case-control study - Report numbers in each exposure category, or summary measures of exposure Cross-sectional study - Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalizability	21	Discuss the generalizability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

[a]Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.