Congenital heart disease confounding the diagnosis of arrhythmogenic right ventricular cardiomyopathy

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy of predominantly the right ventricle (RV) and a cause of sudden cardiac death.¹ Fifty percent of the cases are familial,² with causative gene mutations that primarily affect desmosomes and result in progressive fibro-fatty infiltration of the myocardium.³ In turn, this may lead to ventricular dysfunction and arrhythmias, sometimes causing sudden cardiac death.¹

There is a putative role of RV stress on disease progression, supported by the observation that the development and manifestations of ARVC may be modulated by the frequency and intensity of exercise in heterozygous ARVC carriers.⁴ Even in healthy subjects, chronic strenuous endurance exercise may result in RV dysfunction with a phenotype that is similar to ARVC.⁵

The early diagnosis of ARVC is important to prevent the severe outcomes of unrecognized disease. The 2010 revised Task Force Criteria (rTFC) (Table 1) addresses this issue by increasing diagnostic sensitivity while remaining highly specific.⁶ However, it continues to have limitations, especially in children, where some phenotypic features of ARVC may not yet be expressed.⁷ Furthermore, the differentiation between ARVC and congenital heart disease (CHD) in the pediatric population is important, as treatments and outcomes vary.

We present a series of pediatric patients in whom the clinical presentation has confounded the diagnosis of CHD versus ARVC.

Case report

We reviewed all cases of suspected or confirmed ARVC between the years 1990 and 2012 at 2 tertiary pediatric hospitals in urban centers. We included patients in whom the examination yielded a presumptive diagnosis of ARVC and a final diagnosis of CHD, or vice-versa. The medical charts were reviewed and clinical, electrocardiographic, and imaging data extracted. The results were anonymized, tabulated, and evaluated under the rTFC. A descriptive data analysis was performed for each case.

We identified 4 patients in whom the findings of undiagnosed or seemingly unimportant CHD were initially attributed to ARVC (Table 2). The median age at presentation was 12 years. They shared in common certain findings: RV or right ventricular outflow tract (RVOT) dilation was present in all, pulmonary to systemic blood flow (Qp:Qs) was increased in 2, and significant ventricular ectopy was noted in 2. The final diagnosis was most often partial anomalous pulmonary venous circulation (PAPVC). In contrast, we identified 1 patient in whom mild CHD masked the likely diagnosis of ARVC.

Case 1

An 11-year-old male subject was referred for evaluation of palpitations, incomplete right bundle branch block (IRBBB) on electrocardiogram (ECG), and over 1000 premature ventricular contractions (PVCs) on 24-hour Holter monitor. Family history was positive for consanguinity. ECG showed an IRBBB (QRS duration 100 ms), T-wave inversion, and slightly negative and biphasic T waves in lead V2. Signal-averaged ECG (SAECG) showed prolongation of the filtered QRS duration and a duration of high-frequency, low-amplitude signals that approached the upper limit of normal (Z-score 1.8). There were over 2000 PVCs on 24-hour Holter monitor. Exercise testing and echocardiography were both unremarkable. Cardiac magnetic resonance (CMR) showed a mildly dilated RV with normal contractility. Genetic testing was negative for disease-causing mutations.

At this point, the patient met 2 minor criteria for ARVC and invasive testing was done. Cardiac catheterization with angiography as well as electrophysiology (EP) study were normal. Endomyocardial biopsy yielded subtle mitochondrial changes thought to be noncontributory and inconsistent with ARVC. On follow-up CMR, the RV was moderately

KEYWORDS
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KEY TEACHING POINTS

- Arrhythmogenic right ventricular cardiomyopathy (ARVC) presents a diagnostic challenge in the young, where phenotypic features may be absent and findings may overlap with congenital heart disease (CHD).
- Right ventricular (RV) volume overload secondary to left-to-right shunting may produce arrhythmias and structural abnormalities that mimic ARVC, and at times meet diagnostic criteria.
- RV dilation despite normal systolic function and increased pulmonary to systemic blood flow ratio were important clues of a covert left-to-right shunt. Cardiac magnetic resonance is useful in differentiating nonobvious CHD from a myocardial disease such as ARVC.

A 17-year-old male subject was referred for mild chest pain and closure of an atrial septal defect (ASD). Echocardiogram showed a small ostium secundum ASD measuring 0.9 cm with left-to-right shunt, low RV systolic pressure (28 mm Hg), and normal interventricular septal curvature. The RV was mildly dilated with a parasternal long axis view of the RVOT of 36 mm or 18.38 mm/m² (Z-score of 3.6). This patient fulfilled a major criterion of the original Task Force Criteria and had features of minor criteria of the rTFC on the basis of structural alterations without wall motion abnormality. However, CMR was negative for ARVC. The patient underwent percutaneous ASD closure, which resulted in interval reduction of RV dilation on follow-up echocardiography (Z-score 2.7).

Case 4
A 6-year-old female subject presented for episodic palpitations lasting 30 minutes. Prior evaluation included an echocardiogram showing an ostium secundum ASD, RV and right atrial dilation, and mild mitral regurgitation. Family history was unremarkable. ECG showed normal sinus rhythm with an IRBBB. SAECG showed a prolonged unfiltered QRS duration. Holter monitoring showed rare PVCs and exercise testing induced PVCs of RVOT origin that were suppressed at higher heart rates. A prior ECG had captured a regular narrow-complex tachycardia with a cycle length of 375 ms. She underwent EP study and was found to have dual atrioventricular-nodal physiology. The symptoms persisted despite slow pathway modification. Subsequent echocardiography demonstrated trace localized pericardial effusions around the RV, a 1 cm ASD with left-to-right shunt, and a dilated RV (Z-score 5.34). She was placed on nadolol and underwent percutaneous device closure of the ASD, both resulting in good symptom control.

On routine follow-up at 7 and 10 years of age, she reported episodic syncope. Echocardiography demonstrated persistent RV dilation. CMR showed a right ventricular end-diastolic volume index of 107 mL/m² with wall motion abnormalities and a right ventricular ejection fraction of 43%. The left ventricle had areas of delayed enhancement and myocardial thinning with a mildly reduced ejection fraction. Furthermore, history from collateral confirmed that a maternal grandfather had died of a “heart problem” at 42 years of age.

Despite arrhythmia and CHD requiring EP modification and percutaneous closure, respectively, this patient’s progressive findings raised suspicion of ARVC. Indeed, this patient met a “borderline” diagnosis of ARVC by the rTFC. The patient was exercise restricted. Subsequent genetic testing did not identify any disease-causing mutations.

Case 5
A 13-year-old female subject was referred for exertional palpitations and dizziness. At 18 months of age a cardiac murmur prompted an echocardiogram that was reported as normal. Family history was positive for a father with heart problems in his thirties. There was a systolic murmur and widely split S2 on physical examination. Noninvasive testing yielded an IRBBB on ECG, ventricular bigeminy on Holter monitor, and RV dilation on echocardiography. At this point, ARVC was suspected. Exercise testing also showed ventricular bigeminy in rest and recovery with occasional PVCs. SAECG could not be interpreted owing to frequent PVCs. Repeat echocardiogram again showed significant RV dilation with normal function and the incidental finding of a left superior vena cava draining to the coronary sinus. The pulmonary veins were poorly visualized. Although no obvious shunt was identified,
The 2010 revised ARVC/D diagnostic Task Force Criteria

| Major criteria | Minor criteria |
|----------------|---------------|
| **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 |
| | | PSAX RVOT ≥ 36 mm |
| | | Fractional area change ≤ 33% By MRI |
| | | Regional RV akinesia, dyskinesia, or dyssynchronous RV contraction, and 1 of the following: |
| | | RVEDV-to-BSA ratio ≥ 110 mL/m² (male) or ≥ 100 mL/m² (female) |
| | | RV ejection fraction ≤ 40% By RV angiography |
| **Tissue characterization of wall** | Regional RV akinesia, dyskinesia, or aneurysm |
| | | 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 EMB |
| **Repolarization abnormality** | Inverted T waves in right precordial leads (V1–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–V2 in individuals > 14 years of age (in the absence of complete right bundle branch block) or in V4–V6 |
| **Depolarization abnormality** | Epsilon waves in the right precordial leads (V1–V3) |
| | Late potential by SAEG in ≥ 1 of 3 parameters in the absence of a QRS duration of ≥ 110 ms on the standard ECG |
| | Filtered QRS duration ≥ 114 ms |
| | Duration of terminal QRS < 40 μV or ≥ 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 QRS |
| **Arrhythmias** | Nonsustained or sustained ventricular tachycardia of left bundle branch morphology with superior axis |
| | | By standard ECG |
| | | By Holter |
| | | By ambulatory ECG |
| **Familial history** | ARVC confirmed in a first-degree relative who meets current Task Force Criteria |
| | | ARVC confirmed pathologically in the first-degree relative |
| | | Identification of a pathogenic mutation categorized as associated or probably associated with ARVC |

Adapted from Marcus et al.6

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.

ARVC = arrhythmogenic right ventricular cardiomyopathy; BSA = body surface area; ECG = electrocardiogram; EMB = endomyocardial biopsy; MRI = magnetic resonance imaging; PLAX = parasternal long-axis; PSAX = parasternal short-axis; RV = right ventricle; RVOT = right ventricular outflow tract; SAEG = signal-averaged ECG.

her echocardiographic Qp:Qs estimate was 3:1. Subsequent CMR showed anomalous venous return of the right upper and middle veins to the right superior vena cava. There was also an inferior sinus venous ASD, not well seen on prior imaging owing to the left superior vena cava draining into the coronary sinus (Figure 3). Despite features of ARVC, including RV dilation and ventricular ectopy, this patient’s presentation is best accounted for by PAPVC and ASD. She underwent surgical repair of anomalous pulmonary veins and ASD and has done well on follow-up.

### Discussion

ARVC poses a diagnostic challenge, especially in children, in whom phenotypic features of ARVC may be absent and findings may overlap with CHD. In this series, we describe several cases in which CHD with left-to-right shunting produced findings that mimic ARVC. Most commonly, these findings were arrhythmias and structural abnormalities, including RV and RVOT dilation. According to the rTFC, case 1 met a “definite diagnosis” while cases 2 and 5 met minor diagnostic criteria (Tables 1 and 2).
RV dilation despite normal systolic function and increased Qp:Qs ratio were important clues that the underlying problem was in fact volume overload secondary to covert left-to-right shunts, which were nonobvious on initial echocardiography. Ultimately, CMR proved invaluable in detecting covert CHD. The most challenging of these cases involved anomalous pulmonary venous return.

In contrast, we describe 1 case in which structural abnormalities initially attributed to CHD with left-to-right shunting were ultimately due to ARVC. CMR again proved invaluable in demonstrating RV dysfunction and findings consistent with myocardial disease.

ARVC and CHD at times share the common phenotype of RV dysfunction despite different mechanisms of disease. The pathogenesis of ARVC involves impaired desmosomal function subjected to stress. This is accelerated by conditions such as exercise, which disproportionately increase RV stress. Recent studies suggest that chronic RV stress in an otherwise healthy heart can result in a phenotype similar to ARVC in the absence of impaired desmosomes. We postulate that RV volume overload due to structural CHD with left-to-right shunting in an otherwise healthy heart may also lead to structural and electrophysiologic findings consistent with ARVC. This observation emphasizes the importance of early detection of CHD and offers insight into the pathogenesis of disease.

![Figure 1](image-url)  
**Figure 1** Echocardiogram of case 5 demonstrating an enlarged right ventricle (RV) and a normal left ventricle (LV).
The differentiation between ARVC and CHD is important owing to differences in management and outcomes. Structural CHD may be managed with percutaneous or surgical interventions, and the resultant mortality rates are relatively low. On the other hand, ARVC is managed with activity restriction, medical therapy, and antiarrhythmic therapies when necessary, along with cascade familial screening. With appropriate management, mortality rates in ARVC are also low. We therefore urge the careful evaluation of ARVC versus CHD in children, where phenotypes may overlap and the stakes are high. In keeping with a recent study, we found CMR to be particularly useful for the evaluation of ARVC in the pediatric patient.

Conclusion
This case series demonstrates that pathologies causing RV overload can mimic ARVC, and those with extracardiac shunts may be missed on standard echocardiography. This underscores the importance of ruling out CHD, particularly with left-to-right shunts, before diagnosing ARVC in the young. In our experience, despite a high index of suspicion for ARVC, careful echocardiography, Qp:Qs analysis, and/or CMR are essential to detect covert CHD in the pediatric evaluation of ARVC.
6. Marcus FI, McKenna WI, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D). Circulation 2010;121:1533–1541.

7. Etoom Y, Govindapillai S, Hamilton R, Manlhiot C, Yoo S-J, Farhan M, Sarikouch S, Peters B, McCrindle BW, Grosse-Wortmann L. Importance of CMR within the Task Force Criteria for the diagnosis of ARVC in children and adolescents. J Am Coll Cardiol 2015;65:987–995.

8. Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: trends in the US population from 1979 to 2005. Am Heart J 2009;158:874–879.

9. Schinkel AFL. Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardio-myopathy patient outcomes, incidence of appropriate and inappropriate interventions, and complications. Circ Arrhythm Electrophysiol 2013;6:562–568.