

## Myocardial inflammation detected by cardiac MRI in Arrhythmogenic right ventricular cardiomyopathy: A paediatric case series

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### ABSTRACT

**Introduction:** Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited myocardial disease with an elusive association with myocardial inflammation. A myocarditis phenotype has been well established without systematic evidence of a viral trigger. We intend to study the relationship between myocardial inflammation detected by Cardiac magnetic resonance (CMR) and ARVC in a paediatric population.

**Methods:** Retrospective case series of all patients <18 years admitted to two CMR units for clinical suspicion of myocarditis from March 2012 to June 2017 who had genetic testing for inherited cardiomyopathies including analysis for known ARVC genes.

**Results:** Six patients were identified experiencing myocarditis-like episodes with chest pain and troponin elevation. All had CMR evidence of active myocardial inflammation often affecting the left ventricle without identification of an infectious trigger. These episodes were likely exercise-induced in 50% of our patients and were multiple in all but one.

**Conclusion:** We provide evidence that ARVC can present as recurrent myocarditis-like episodes with CMR evidence of myocardial inflammation despite absent infectious trigger in children. We believe they represent an active *hot phase* of the disease and may lead to disease progression.

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### 1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited myocardial disease characterized by cardiomyocyte atrophy and fibro-fatty replacement, with an overall reported prevalence of 1/1000 to 1/5000 [1–3]. The disease usually presents in young adults and adolescents and is an important cause of ventricular tachycardia and heart failure in this age group [1]. It is one of the leading causes of sudden cardiac death (SCD) in the young, accounting for up to 11% of SCD (22% among the athletes) under the age of 35 years in some regions of the world [4].

The mechanisms of the disease are still debated [5]. Historically, an inflammatory theory, based on the histopathological finding of myocarditis in endomyocardial biopsies of these patients [6–11],

suggested a possible viral trigger in the process of the disease [12]. However, systematic myocardial viral RNA research failed to support this hypothesis [13]. Abnormal apoptosis seems to be implicated, as it is observed in tissue samples from living patients [14] and correlates with abrupt onset of the disease as well as acuteness of symptoms [15]. The identification of causal genes coding for desmosomal proteins [16–21] has shed light into the possible pathophysiological role of tissue fragility.

Electroanatomic map-directed endomyocardial biopsies of a series of ARVC patients have shown either features of myocarditis-like inflammation or typical fibrofatty replacement [22], possibly reflecting different stages of the disease. In fact, recent evidence suggests that adults may experience rather abrupt progression of the disease presenting as a myocarditis-like “hot phase” characterized by troponin rise and myocardial inflammation [23–25].

Paediatric evidence of such disease behaviour is insufficient, with only a few cases reported [6,23,26], only one of which fulfilling CMR criteria for myocardial inflammation [26].

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**Table 1**  
Patients characteristics.

Patient	Gender	Age at admission (years)	Follow-up (years)	Family history	Number of myocarditis-like episodes	Gene	ECG during myocarditis-like episode	ECG during follow-up	NYHA at last follow-up
1	F	11	8	Yes	6	DSG2	Ti V1–2	Unchanged	I
2	M	15	7	No	3	PKP2	Ti V1–3	Unchanged	I
3	M	5	1	No	2	DSP	Arrhythmic storm with RBBB VT	Normal	Transplant
4	M	10	6	Yes	1	DSP	Unspecific QRS prolongation	Epsilon wave	I
5	M	12	3	Yes	2	PKP2	Right precordial STe and Ti; LBBB VT	Ti V3–6 and inferior limb leads	II
6	M	2	Death	No	2	DSP	Normal	Unchanged	Death

LBBB – Left bundle branch block. NYHA – New York Heart Association functional class. RBBB – Right bundle branch block. STe – ST segment elevation. Ti – T wave inversion. VT – Ventricular tachycardia.

In this paper, we sought to study the relationship between myocardial inflammation detected by cardiac magnetic resonance (CMR) and ARVC in a paediatric population.

## 2. Population and methods

We retrospectively reviewed all patients <18 with a clinical and genetic diagnosis of ARVC which had previously been admitted to two CMR Units for clinical suspicion of myocarditis from March 2012 to June 2017.

A complete diagnostic evaluation including full echocardiography according to TASK Force criteria [27,28] for ARVC was performed in all patients.

All living patients are still under continued follow-up at our outpatient clinics.

### 2.1. CMR imaging

Cardiac magnetic resonance was performed using a 1.5 Tesla magnet (MR450 GE Medical systems, Milwaukee, USA). Images were acquired with a 32-channel phased-array cardiac coil and a vector electrocardiogram for R wave triggering using a standard CMR imaging protocol.

The criteria that we used to diagnose myocardial inflammation were: [29,30] 1) evidence of regional or global myocardial oedema with T2 hyperintensity (T2 ratio > 2, where T2 ratio = Signal intensity<sub>myocardium</sub> / Signal intensity<sub>skeletal muscle</sub>); 2) evidence of myocardial hyperaemia and capillary leak with early gadolinium enhancement (EGE) on cine-SSFP and/or T1-weighted images (acquired early after contrast injection) as compared to the skeletal muscle; or 3) evidence of myocardial necrosis and fibrosis (visual assessment) with non-ischemic regional distribution at late gadolinium enhancement (LGE) imaging. The evaluation of EGE was done on cine-SSFP sequence (visual assessment) as previously reported [31] soon after contrast injection. Myocardial inflammation was diagnosed when at least two criteria were present.

**Table 2**  
CMR results at admission and follow-up.

Patient	Age at first CMR (years)	LV EF at first CMR	T2 criteria	EGE criteria	LGE criteria	LV localization	Last CMR at follow-up	RV compromise at follow-up	Last LV EF
1	11	55%	Yes	Yes	Yes	Septal basal	RV and LV septal fibrosis	Right ventricular fibrosis without ARVC criteria	55%
2	15	65%	Yes	Yes	Yes	Lateral	Normal	RV dyskinesia on ventriculography and fibrosis at biopsy	55%
3	5	23%	No	Yes	Yes	Anterior, lateral, apical	NA	Dilatation and severe dysfunction	15%
4	10	60%	No	Yes	Yes	lateral	ARVC major criteria	Dilatation and dysfunction	54%
5	12	53%	Yes	Yes	Yes	Anterior, lateral, apical	ARVC major criteria	Dilatation and severe dysfunction	42%
6	2	20%	Yes	Yes	Yes	Anterior, lateral, apical	NA	NA	NA

EF – ejection fraction; EGE – early gadolinium enhancement; LGE – late gadolinium enhancement; LV – left ventricle; RV – right ventricle.

### 2.2. Genetic analysis

Genetic analysis was performed using Next Generation Sequencing method (GS) and analysed with Genodiag. Sanger method was then used to validate the variant identified by NGS. The panel of genes analysed was: PKP2, DSC2, DSG2, DSP, LMNA, RYR2.

## 3. Results

Six patients were eligible for our study. Their characteristics are summarized in Table 1 and respective CMR data are summarized in Table 2. Genetic data is available in Supplementary table 1.

*Patient 1* was asymptomatic until the age of 11 years, when she had a first episode of chest pain, troponin elevation (13 ng/mL) and CMR evidence of subepicardial myocardial inflammation. Acute myocarditis associated with Coxsackie virus infection was diagnosed based on serologic data. Her father had been previously diagnosed with ARVC, with biventricular dysfunction, and had required ICD placement after resuscitated sudden death. Genetic screening was performed and showed that she inherited paternal DSG2 mutation for ARVC.

Subsequently, she experienced a total of six recurrent chest pain episodes during 8 years of follow-up, always with concomitant significant troponin elevation but without evidence for viral infection. CMR evidenced myocardial inflammation during three of these episodes of chest pain. Evidence of fibrofatty infiltration in the septal and lateral segments of the left ventricle was first noted at CMR at the age of 14 years and associated with wall thinning of the right ventricle in the last study at the age of 17 years. Beta-blockers (nadolol) were started from the age of 16 years. Ventricular function remained good and no ventricular arrhythmias were noticed during follow-up.

*Patient 2* presented at the age of 14 years with a self-limited episode of exercise-induced chest pain without palpitations but with transient troponin rise. He had no relevant familial history, normal ECG (except for negative T waves on right precordial leads) and normal echocardiographic evaluation, so he was discharged without further investigation. The recurrence of symptoms at the age of 16 years with isolated

ventricular premature beats elicited a CMR. Acute myocarditis was identified, with left ventricular septal and lateral subepicardial inflammation. No contemporary viral infection could be found. He was treated with beta-blockers. A few months later, he had another exercise-induced chest pain episode, with palpitations and syncope as well as troponin rise (2 ng/mL). CMR was repeated and showed persisting signs of diffuse subepicardial myocardial inflammation. CMR controls at 3 and 6 months showed persistent septal and lateral LGE compatible with fibrosis, but with preserved biventricular function. Elective diagnostic cardiac catheterization was performed at the age of 18 years. Right ventriculography demonstrated abnormal regional motion and right ventricular biopsies revealed non-inflammatory myocardial fibrosis. ARVC was suspected and confirmed by genetic analysis of ARVC genes showing a PKP2 mutation.

*Patient 3* was admitted at the age of 3 years, following routine cardiac examination as part of the investigation of cutaneous disease with atrichia and palmoplantar keratoderma suggestive of desmosomal disease. CMR showed biventricular dilatation and dysfunction with diffuse subepicardial inflammation (Fig. 1A and B). Genetic analysis confirmed a DSP mutation compatible with Carvajal syndrome. A few months later, he was readmitted for severe ventricular arrhythmia that pushed him to the edge of mechanical circulatory assistance (Supplementary fig. 1). He completely recovered, and an ICD was implanted. At the age of 5 years, he had two exercise-induced syncope episodes without recorded events on ICD interrogation. Both episodes were characterized by transient elevation of troponin levels followed by progressive deterioration of echocardiographic cardiac function (Fig. 2A). He was successfully transplanted in December 2017.

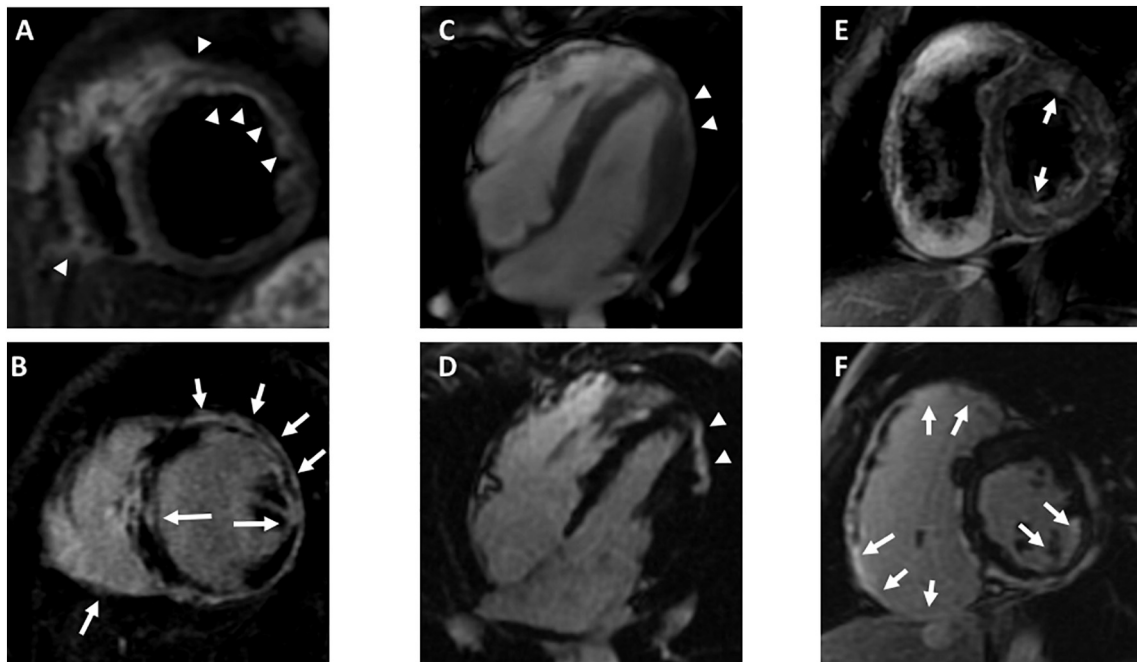
*Patient 4* was admitted at the age of 10 years for atypical chest pain with transient troponin elevation (max 64 ng/mL). CMR showed signs of acute myocarditis, with myocardial inflammation on the lateral left ventricular wall without dysfunction. He received a short course of steroids and was treated with beta-blockers. Six months later, control CMR revealed LGE of the right ventricular free wall compatible with fibrotic changes, without evidence of active inflammation. His father had previously been diagnosed with Naxos syndrome with typical cutaneous

phenotype and ARVC requiring ICD implantation. Patient shared the same cutaneous phenotype and inherited the same DSP mutation.

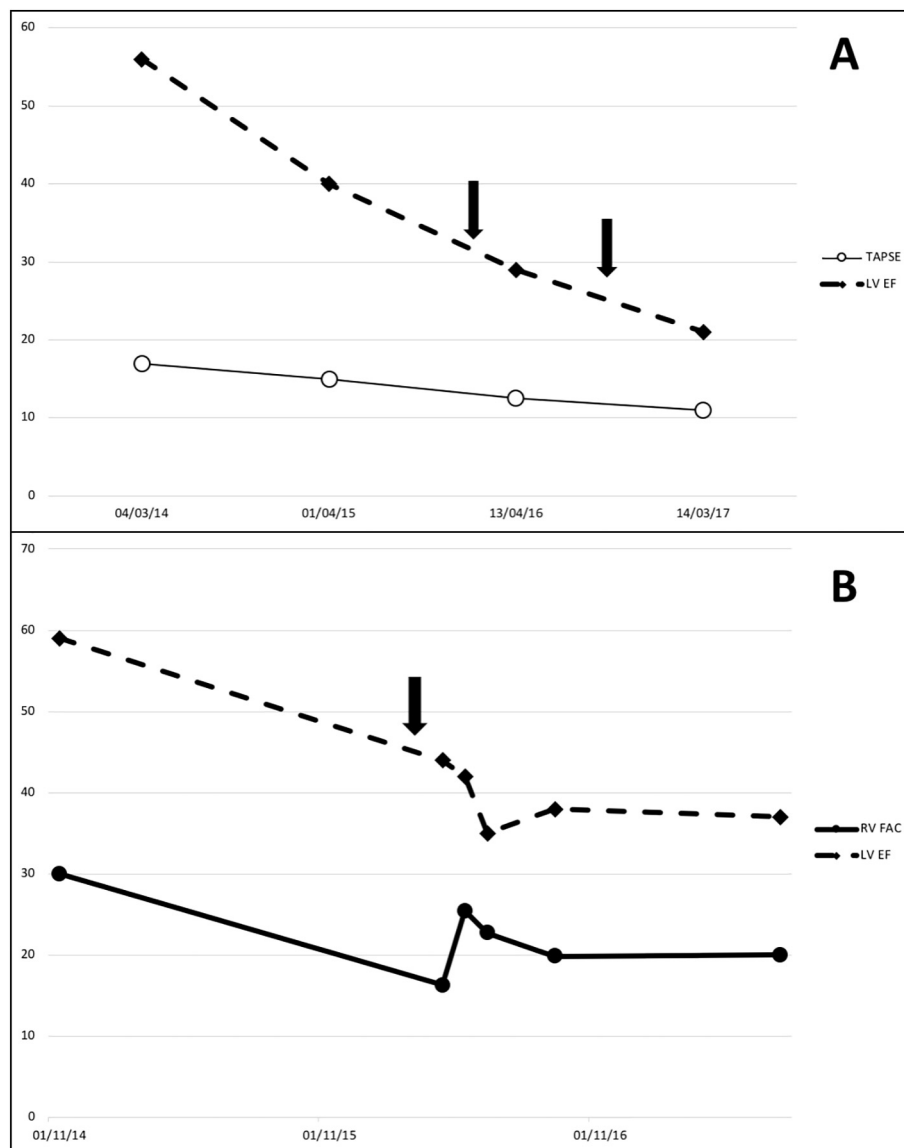
Recent control CMR (5 years after first CMR) showed typical signs of ARVC according to the Task Force criteria [27], with right ventricular dilatation and dysfunction (right ventricular ejection fraction (EF) 33%, right ventricular end-diastolic volume 133 mL/m<sup>2</sup>) and small dyskinetic regions in the infundibulum corresponding to areas of signal hyperintensity in the T1 weighted black blood sequence, suggestive of fibrofatty infiltration. The patient remains asymptomatic to date without treatment.

*Patient 5* was admitted at the age of 12 years with acute chest pain, palpitations and presyncope. Ventricular tachycardia was identified, which resolved spontaneously after vomiting. He had a family history of myopericarditis (mother and aunt). His ECG in sinus rhythm showed abnormal repolarization pattern with ST depression and inverted T waves in V3–V6. Troponin levels were high at 23 ng/mL. Echocardiography noted a slightly depressed LV function with full recovery the following day. CMR showed subepicardial apical and anterolateral inflammation (Fig. 1C and D) as well as right ventricular dilatation and dysfunction (RVEF 35%). No infectious aetiology was found. He was treated with beta-blockers with subsequent addition of flecainide due to frequent ventricular premature beats. Genetic testing showed a PKP2 mutation. He remained asymptomatic until the age of 14 years when he had another episode of chest pain, LBBB ventricular tachycardia (Supplementary fig. 1) and troponin elevation. CMR performed during this second episode confirmed criteria for ARVC diagnosis [27], with severe RV dilatation and dysfunction (EF 19%) as well as LV dysfunction (EF 41%) associated with evidence of infero-lateral inflammation (Fig. 1E). LGE revealed fibrotic transformation of most of RV free wall as well as LV antero-latero-inferior walls (subepicardial for the most part, transmural in lateral segment – Fig. 1F). An ICD was implanted at this stage, which has delivered several anti-tachycardia pacing and one appropriate shock for ventricular tachycardia to date. He has persistent LV systolic dysfunction with LVEF of 48% (Fig. 2B).

*Patient 6* was admitted at the age of 32 months for respiratory distress and fever. ECG was normal. Troponin levels were elevated (up



**Fig. 1.** CMR evidence of cardiac inflammation. In patient 3 a T2-weighted black-blood imaging (triple inversion recovery sequence) short-axis view (A) displaying subendocardial anterolateral hypersignal, as well as subepicardial anteroseptal and right ventricle free wall hypersignal (arrowheads). The same short axis (B) view displaying anterolateral LGE, transmural in its lateral aspect, as well as RV free wall LGE (arrows). In patient 5 the initial CMR displaying subepicardial LV apicolateral EGE (C, arrowheads) and LGE (B, arrowheads). A second CMR taken 4 years later displaying evidence of focal subendocardial edema (C, arrows) on T2-weighted black-blood imaging (triple inversion recovery sequence), as well as posterolateral and RV free wall LGE (D, arrows).



**Fig. 2.** Evolution of right and left ventricular function and myocarditis-like events (arrows). A) In patient 3, dashed line represents left ventricular ejection fraction (LVEF, in %) and continuous line represents tricuspid annular plane systolic excursion (TAPSE, in mm). B) In patient 5, Dashed line represents left ventricular ejection fraction (LV EF, in %) and continuous line represents right ventricle fractional area change (RV FAC, in %).

to 4 times the normal upper limit). Echocardiogram showed severe left ventricular dilation and dysfunction (LVEF 25%). CMR evidenced active myocardial inflammation of the anterior and lateral left ventricular walls. Acute myocarditis was diagnosed with no evidence of concurrent viral infection. He received human immunoglobulins as well as a short course of steroids. Heart failure therapy was initiated with good clinical response, allowing hospital discharge after 7 days. A homozygous DSP mutation was found. He was readmitted at the age of 36 months with cardiogenic shock and intraventricular thrombus. Unfortunately, no signs of recovery were found after four weeks of mechanical circulatory support. In the absence of a transplantation project due to social reasons, mechanical circulatory support was withheld, and the patient died.

#### 4. Discussion

This is the first series of paediatric patients with genetic diagnosis of ARVC and evidence of myocardial inflammation at CMR.

All six study patients experienced myocarditis-like episodes, characterized by chest pain and significant albeit transient troponin elevation.

They represent a significant part of the total cohort of 21 paediatric patients followed at our two centres for ARVC meeting diagnostic criteria.

CMR clearly revealed active myocardial inflammation with positive criteria for acute myocarditis in all cases. None of the patients had clinical evidence of infection preceding these episodes except for one episode in patient 1 in whom Coxsackie virus serologic testing was positive. This finding supports the concept that these myocarditis-like episodes are active phases of the disease rather than translating genetic susceptibility to infection. These inflammatory episodes seem to accelerate the progression of the disease and lead to subsequent alterations in biventricular morphology and function, in a complex interplay of inherent tissue fragility, apoptosis and inflammation leading to fibrosis and remodelling [23,24].

We have insufficient data to specify a probable trigger for these episodes. Nevertheless, some episodes seemed to be triggered to some extent by exercise (in patients 1, 2 and 3), suggesting genetic susceptibility to effort-induced damage as a possible trigger.

These myocarditis-like episodes were multiple in 5/6 patients, suggesting that a diagnosis of an underlying cardiomyopathy such as ARVC should be considered in the presence of recurrent myocarditis. It

is of note that the occurrence of acute myocarditis has been associated with the progression of myocardial dysfunction in other inherited cardiomyopathies, such as left ventricular non-compaction, and Duchenne muscular dystrophy associated dilated cardiomyopathy [32–37].

Finally, genetic mutations (DSG2, DSP and PKP2) identified in our patients differ from those previously identified in adults (DSP, LDB3) [23] with similar myocarditis-like phenotype, hinting this might be a more generic characteristic of the disease, not related to a specific gene.

## 5. Conclusion

We provide evidence that ARVC can often present as recurrent myocarditis-like episodes with evidence of myocardial inflammation at CMR in children and adolescents. These episodes have no association with infectious triggers, rather seeming to be triggered to some extent by effort. We believe they represent an active *hot phase* of the disease and may lead to disease progression.

## 6. Limits of the study

Limits of our study are based on its retrospective nature. Genetic analysis and cardiac MRI were made in the majority of cases of recurrent myocarditis, but not routinely in all children presenting with myocardial inflammation, so we may have missed some genotype-positive patient. A prospective study that includes all patients with myocardial inflammation at MRI and genetic analysis to detect the eventual appearance of major criteria for ARVC during follow up will be useful.

## Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.05.116>.

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