Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2024 [Online ahead of print]

To cite this Article:
Gomes Tinoco M, Castro M, Pinheiro L, et al. **"Hot phase" clinical presentation of biventricular arrhythmogenic cardiomyopathy: when the perfect electrical storm spontaneously stops.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2024.3086

"Hot phase" clinical presentation of biventricular arrhythmogenic cardiomyopathy: when the perfect electrical storm spontaneously stops

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Contributions: MGT, MC, wrote the manuscript, with contributions from LP, TP, MO, SR, and NF. OA, AL, reviewed the final version of the manuscript. All authors participated in the development of the manuscript and approved its final version.

Conflict of interest: the authors declare no potential conflicts of interest.

Ethics approval and consent to participate: this case report adheres to the ethical standards outlined in the Declaration of Helsinki.

Patient consent for publication: the authors confirm that consent for submission and publication of this case report including images and associated context has been obtained from the patient in line with COPE guidance.

Funding: the authors received no financial support for the research, authorship, and/or publication of this article.

Availability of data and materials: data available from the corresponding author.

ABSTRACT

An 18-year-old male presented with syncope during a training break. Post-syncope, he developed effort dyspnea, which he associated with the Pfizer-BioNTech COVID-19 vaccine received a week earlier. Electrocardiogram showed T inversion in V1-V3, III, and aVF, while 24-hour Holter monitoring revealed frequent ventricular premature beats. A transthoracic echocardiogram showed severe biventricular dilation and mild left ventricular (LV) dysfunction. Cardiac magnetic resonance (CMR) imaging confirmed these findings, showing moderate right ventricular (RV) systolic dysfunction with akinesia of the inferior and inferolateral walls. T2 hypersignal in the middle segment of the inferior inferior interventricular septum suggested myocardial edema. Extensive transmural late gadolinium enhancement was noted in the RV and LV walls. An implantable loop recorder was implanted. Three months later, the patient was admitted with palpitations, fever, and a positive SARS-CoV-2 test. Sustained ventricular tachycardia (VT) episodes were documented and managed with amiodarone and β-blockers. Follow-up CMR showed a slight improvement in LV ejection fraction and resolution of edema. A single-chamber implantable cardioverter-defibrillator (ICD) was implanted. Genetic testing for arrhythmogenic RV cardiomyopathy (ARVC) was negative, and family screening was normal. Two years later, pre-syncope episodes occurred, and ICD interrogation revealed nonsustained VT. The patient is awaiting VT ablation.

This case highlights the diagnostic and therapeutic challenges of ARVC, particularly in differentiating it from myocarditis. The "hot-phase" presentation, vaccine association, and subsequent SARS-CoV-2 infection added complexity. CMR was crucial for diagnosis, and VT management required a combination of medical therapy and invasive procedures.

Key words: arrhythmogenic right ventricular cardiomyopathy, electrical storm, myocarditis, COVID-19 infection and vaccination.

Introduction

The term "arrhythmogenic right ventricular cardiomyopathy" (ARVC) was initially used by physicians who discovered the disease before the genetic and cardiac magnetic resonance imaging (CMR) era. It described a heart muscle disease primarily affecting the RV, characterized by the occurrence of malignant ventricular arrhythmias and fibro-fatty replacement of the myocardium [1].

ARVC can occur in up to 20% of individuals, particularly in young athletes who may experience life-threatening tachyarrhythmias [2]. Therefore, early detection is crucial. Differential diagnosis from acute myocarditis or post-myocarditis scar requires a thorough medical history, clinical family screening, careful analysis of ECG and imaging abnormalities, and genetic testing [2].

Case Report

This clinical case is about an 18-year-old male student, who regularly participated in football and athletics, and had no previous relevant medical or family history. He also denied any history of smoking, alcoholism, or illicit drug use.

He experienced his first episode of syncope, which was preceded by blurred vision and dizziness while he was sitting on the bench during a training break. Following the syncope, he noticed a new onset of effort dyspnea, which he associated with receiving the second dose of the Pfizer-BioNTech COVID-19 vaccine 1 week earlier.

ECG showed a high R wave in V1-V2, inverted T wave in V1-V3, III, and aVF, along with a Q wave in I and aVL, and a pair of ventricular premature beats (VPB) (Figure 1).

A 24-hour Holter monitoring showed sinus rhythm with an average heart rate of 87 bpm and frequent VPBs (5670).

Transthoracic echocardiogram (TTE) revealed severe biventricular dilation and mild left ventricular (LV) systolic dysfunction. He was evaluated by a cardiologist and started therapy with bisoprolol 2.5mg once daily (od) and ramipril 2.5mg od.

CMR confirmed severe dilation of both ventricles and mild LV systolic dysfunction (ejection fraction (EF) of 42%). There was hypokinesia of the mid to distal segments of the anterolateral and inferolateral walls, as well as the distal segment of the anterior wall. Additionally, there was moderate RV systolic dysfunction (RVEF of 34%) with global hypokinesia and akinesia of the inferior and inferolateral walls, as well as the basal lateral segment. The CMR also revealed a T2 hypersignal in the middle segment of the inferior interventricular septum (IVS) on the RV side, suggestive of myocardial edema. There was midmural late gadolinium enhancement (LGE) involving the LV inferolateral and anterolateral walls, as well as the distal segment of the

anterior wall and the RV side of the basal-mid inferior IVS. Additionally, there was extensive transmural LGE in the inferior and lateral walls of the RV (Figures 2 and 3; Videos 1 and 2)

Laboratory data showed no increase in inflammatory parameters, but pBNP was elevated (973 pg/ml, Normal range (NR) <125 pg/ml) and there was a 4-fold elevation in high-sensitivity troponin I levels (211ng/L, NR <45 ng/L).

The diagnostic hypotheses considered were a subacute phase of myocarditis with extensive fibrosis and residual myocardial inflammation; arrhythmogenic cardiomyopathy (ACM) with biventricular involvement; or myocarditis in a patient previously affected by ARVC.

Beta blocker was titrated and the patient was strongly advised to discontinue high and moderate intensity exercise until a definitive diagnosis was made. An implantable loop recorder (ILR) was implanted and a genetic testing for ARVC was requested.

Three months later, the patient was admitted to the Emergency Department following two episodes of palpitations, without syncope, at rest. He also complained of fever and odynophagia.

ECG was superimposable, except for the finding of a triplet of VPB with complete left bundle branch block (LBBB) morphology and superior axis. TTE findings were also superimposable. Laboratory results showed an elevated c-reactive protein (36 mg/L, NR <3 mg/L) and a high-sensitivity troponin I (810 ng/L); and SARS COV2 test was positive. The patient was admitted to the cardiac intensive care unit.

In the first 12 hours of hospitalization, four episodes of sustained monomorphic ventricular tachycardia (VT), lasting a maximum of 2 minutes, were detected and associated with palpitations. Amiodarone infusion was started and beta blocker titrated to the maximum tolerated dose.

Upon reviewing the ILR, we observed 3 episodes of wide complex tachycardia: one episode initiated by a VPB, another episode of very rapid monomorphic VT that appears to change morphology and transitions into polymorphic VT, and another episode with 2 distinct morphologies (Figure 4).

During the hospital stay, the patient switched to oral amiodarone, successfully eliminating dysrhythmic events. However, further therapy titration was limited by the patient's hypotensive profile.

CMR was performed during hospitalization (3 months later from the first one) and showed a slight improvement in LVEF from 42% to 45%. No additional areas of high signal suggestive of myocardial edema were identified in the T2-weighted (STIR) images, and resolution of edema was observed in the inferoseptal wall. The distribution of LGE remained the same (Video 3; Figures 5 and 6)

A single-chamber implantable cardioverter-defibrillator (ICD) was implanted.

The patient was discharged with optimized medical therapy and oral amiodarone. Weeks later, the genetic testing for ACM came back negative.
Regarding family screening, the patient's brother, father, and mother all had normal TTE and ECG.
Two years later, the patient had an episode of pre-syncope. He was medicated with bisoprolol 10 mg od and amiodarone 200 mg od. The ICD was interrogated, and two episodes of NSVT with 32 and 48 complexes were detected at the time of the symptoms. The patient is currently awaiting VT ablation.

Discussion and Conclusions

We present an ARVC case with a clinical presentation of a “hot-phase” and ventricular dysrhythmias.
The definitive diagnosis of ARVC was based on the presence of three major criteria of the revised Task Force criteria: regional RV akinesia, global RV dilatation and systolic dysfunction, inverted T waves in right precordial leads (V1, V2, and V3), frequent VPB (>5000) and non-sustained/sustained VT with a LBBB morphology and superior axis [3].
Furthermore, according to the Padua criteria, the patient also met major criteria for LV involvement, including global LV systolic dysfunction, dilatation and LGE in at least one bull's eye segment, as well as minor criteria like regional LV hypokinesia [4]**.** However, these criteria are still awaiting external validation [1].
A detailed evaluation of ACM is crucial, as there are three phenotypes with significant diversity in clinical expression and outcomes: ARVC, LV ACM, and biventricular ACM. ARVC and biventricular ACM have a higher incidence of life-threatening ventricular arrhythmias. Biventricular ACM shows more heart failure, need for heart transplantation, and cardiovascular mortality. LV ACM has more "hot phases" [5]. Our patient presents with a biventricular form.
Differential diagnosis between ARVC and myocarditis can be challenging, as some patients with ARVC can present with bouts of acute or subacute myocarditis, characterized by episodes of chest pain and palpitations, troponin release and myocardial edema on CMR. These "hot phases" may occur as the first manifestation of the disease or later during the clinical course as an expression of the disease progression [2].
A multimodality imaging approach, including TTE and CMR, is crucial for diagnosis, risk stratification, monitoring, and intervention in ARVC, improving patient outcomes and helping prevent sudden cardiac death (SCD). Echocardiography is useful in both initial and advanced stages, enabling earlier diagnosis, providing prognostic information, and is preferred for follow-up. CMR is a fundamental tool, offering not only morphological and functional assessment but also tissue characterization. While fibro-fatty substitution is a histological hallmark of ARVC,

CMR can also detect inflammation, myocyte necrosis, and edema, which are characteristic features in a myocarditis-like clinical presentation. The strategic use of these methods aids in confirming ARVC, differentiating it from other conditions, and tracking disease progression, facilitating informed and personalized clinical decisions [6]. In some cases, endomyocardial biopsy may be helpful, especially in sporadic forms, although its risk/benefit ratio is still unknown and it is not usually indicated for ARVC diagnosis [1].

In the differential diagnosis between the "hot phase" of ARVC and acute myocarditis, a family history of SCD and/or ARVC can be crucial [5,7]. However, in this case, the absence of such a history and a negative genetic test made the diagnosis particularly challenging. The association of "hot phases" with the Pfizer-BioNTech COVID-19 vaccination and COVID-19 infection added further complexity. We also need to consider the possibility of myocarditis in a patient who has previously been affected by ARVC. COVID-19 has increased the incidence of myocarditis by at least 15 times compared to pre-COVID levels, with an incidence ranging from 150 to 4000 cases per 100000 individuals. The incidence of COVID-19 vaccine-associated myocarditis varies widely depending on the vaccine platform, age, and sex. Notably, it predominantly occurs in male patients aged 12 to 40 years, regardless of whether the cause is a virus like SARS-CoV-2 or associated with a vaccine [8], a demographic similar to ARVC, as seen in our patient.

This case highlights the challenge of treating VT in ARVC. The average risk of VT in ARVC ranges from 3.7 to 10.6% per year, often well tolerated without leading to SCD, as seen here. We should consider that COVID-19 infection or vaccination could trigger arrhythmias [9,10], especially in patients with ARVD.

Beta-blockers are the first-line treatment to reduce arrhythmic events. Amiodarone is used when beta-blockers fail, and flecainide is considered when single-agent treatment is insufficient. Some patients require invasive procedures and/or ICD implantation, as in our case. Our patient had high-risk features such as arrhythmic syncope, NSTV, LVEF<45%, and a 40% risk of fast VT/VF/SCD at 5 years according to the risk-prediction model (arvcrisk.com), which led to the decision to implant an ICD. He was referred for VT ablation due to persistent symptomatic NSVT despite medical therapy, as this procedure can help reduce VT burden [1].

In summary, this case illustrates the diagnostic and therapeutic challenges of ARVC, namely the differential diagnosis between a hot phase of ARVC and myocarditis and the treatment of VT.

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Online supplementary material:
Video 1. Cine short axis showing severe biventricular dilation and impairment of biventricular systolic function.
Video 2. Four chambers view showing severe biventricular dilation and impairment of biventricular systolic function.
Video 3. Cine 4 chambers showing severe biventricular dilation, with slight impairment of left ventricular systolic function and moderate impairment of right ventricular systolic function.

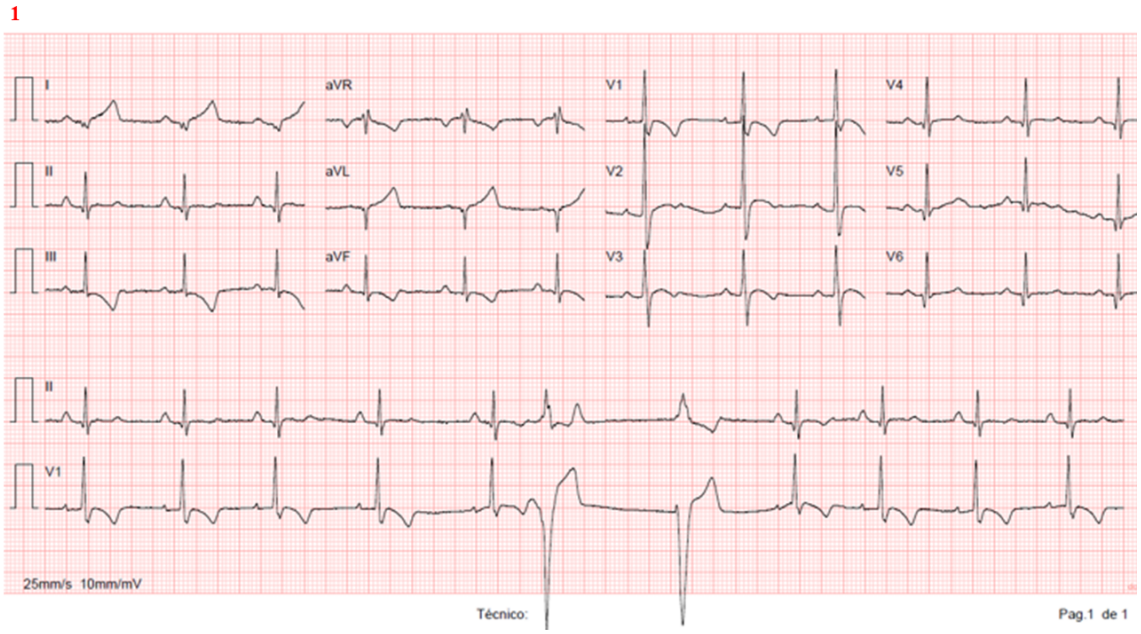

Figure 1. ECG showing a high R wave in V1-V2, inverted T wave in V1-V3, III, and aVF, along with a Q wave in I and aVL, and a pair of ventricular premature beats.

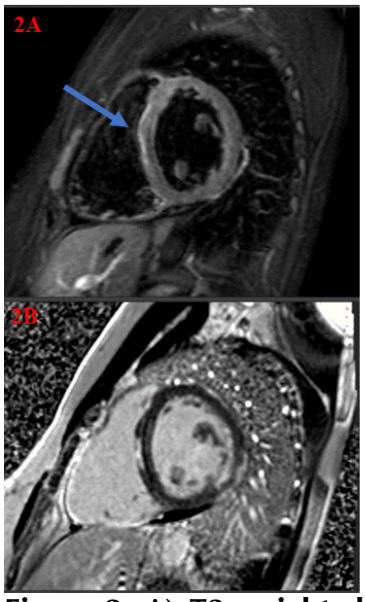

Figure 2. A) T2-weighted (STIR) short axis showing T2 hypersignal on the RV side of the middle segment of the inferior interventricular septum; B) LGE in same location.

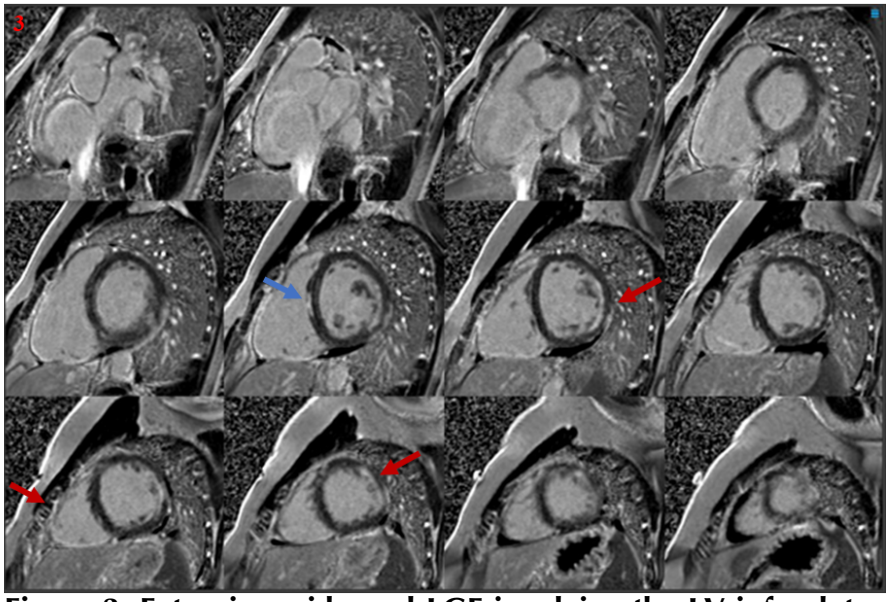

Figure 3. Extensive midmural LGE involving the LV inferolateral and anterolateral walls, as well as the distal segment of the anterior wall and the RV side of the basal-mid inferior IVS. Additionally, there was extensive transmural LGE in the inferior and lateral walls of the RV.

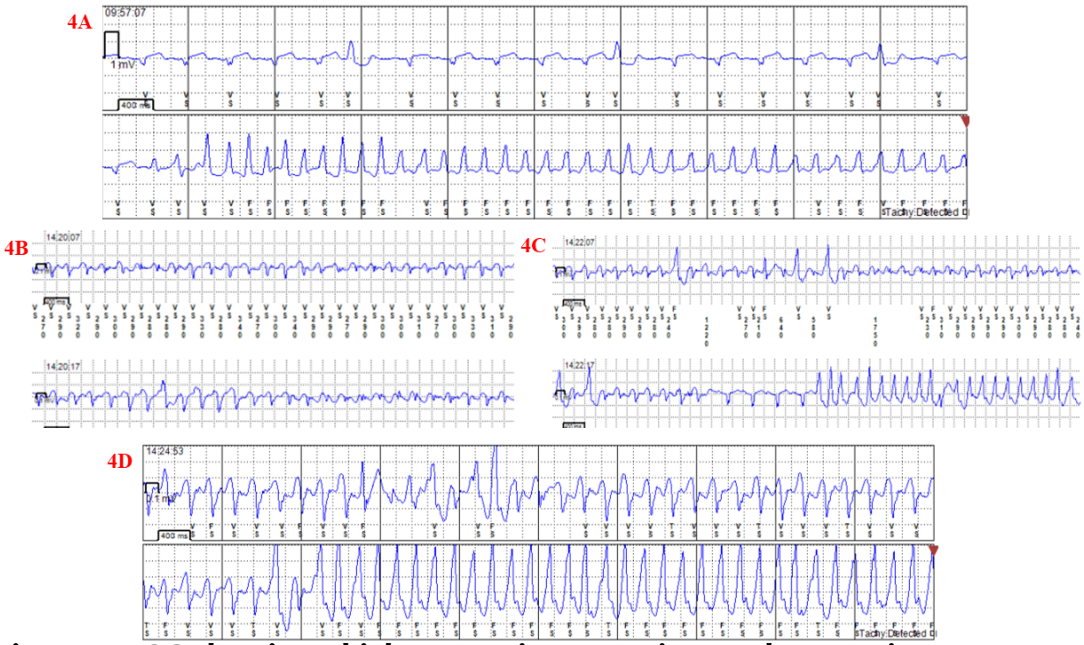

Figure 4. ECG showing a high R wave in V1-V2, inverted T wave in V1-V3, III, and aVF, along with a Q wave in I and aVL, and a triplet of ventricular premature beats with LBBB morphology and superior axis.

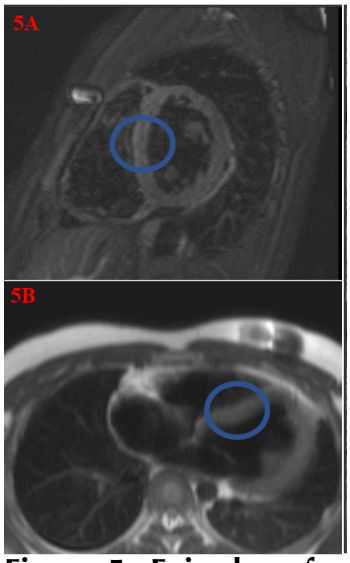

Figure 5. Episodes of wide complex tachycardia; 5A: episode initiated by a ventricular premature beat; 5B-C: episode of very rapid monomorphic ventricular tachycardia that appears to change morphology and transitions into polymorphic ventricular tachycardia; 5D: another episode with 2 distinct morphologies.

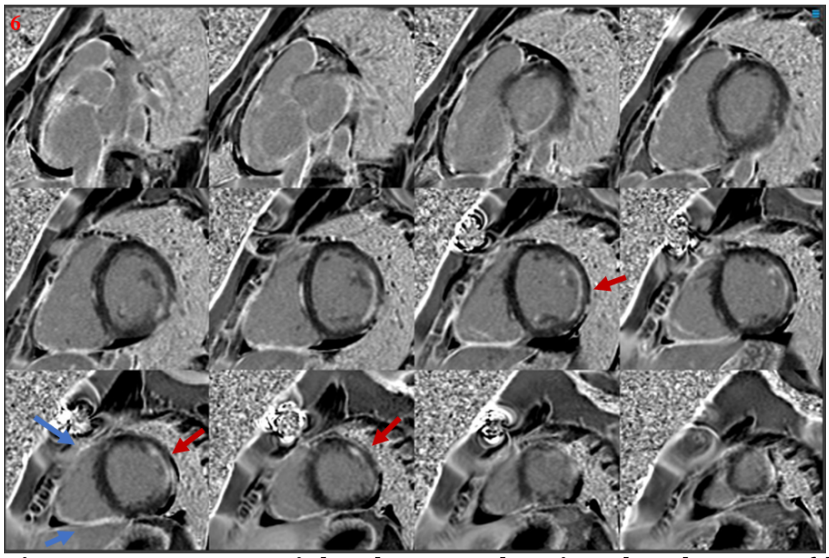

Figure 6. A,B) T2-weighted (STIR) showing the absence of hypersignal on the RV side of the middle segment of the inferior interventricular septum three months later.