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CASE REPORT
Heart failure

How exercise can deteriorate the clinical course of an ARVC patient: a case report

Enzo Lüsebrink [1,2†], Leonhard Binzenhöfer[1,2†], Stefan Brunner[1,2], Jörg Hausleiter[1,2], Steffen Massberg [1,2], Martin Orban[1,2‡], and Stefan Kääb [1,2,*,‡]

[1]Department of Medicine I, University Hospital, Ludwig-Maximilians University Munich (LMU), Marchioninistrasse 15, 81377 Munich, Germany; and [2]DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

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Background Arrhythmogenic right ventricular cardiomyopathy (ARVC)/dysplasia is a genetic disease characterized by fibro-adipose degeneration of ventricular myocardium. Initial clinical presentation is variable and ranges from asymptomatic cases to chronic heart failure and sudden cardiac death due to malignant arrhythmias.

Case summary Here, a 67-year-old male patient who started extensive physical training upon retirement and presented with ventricular tachycardia and progressive heart failure as a first sign of his disease. Arrhythmogenic right ventricular cardiomyopathy diagnosis was established according to the 2010 modified Task Force Criteria and supported by HRS/EHRA consensus-based genotyping. After initial discharge on optimal medical therapy and prophylactic implantable cardioverter-defibrillator implantation according to his individual ARVC risk score, the patient reported rapid decline in physical capacity on a regular follow-up 4 months later. To better understand the aetiology of his clinical deterioration, we performed stress echocardiography, coronary angiogram, and exercise right heart catheterization, which conclusively suggest impaired left ventricular filling secondary to right ventricular failure as a main cause of global circulatory failure.

Discussion The present case report focuses on relation of physical activity to disease onset and the concomitant advent of symptoms during exercise as well as a structured and guideline-aided diagnostic workup in ARVC and staged treatment options. Continuous ARVC centre-oriented re-assessment and treatment planning including lifestyle intervention, psychological support, medical, surgical, and interventional options are key elements of sustained long-term care for ARVC patients.

Keywords ARVC • Dyspnoea • Right heart failure • Tricuspid valve insufficiency • Case report

Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is an inherited disease characterized by replacement of myocardium by fibro-adipose tissue with arrhythmic potential.[1–3] In Europe, the estimated prevalence ranges from 1:5000 to 1:2500 cases per persons with a cardiac mortality rate of 0.9% per year.[3,4] Degeneration of right ventricular (RV) singular ectopic beats into ventricular tachycardias is often triggered by adrenergic stimulation, making physical exertion a risk factor for sudden cardiac death (SCD) in patients.[5–7] Ever since ARVC diagnostic guidelines were first published in 1994,[8] new imaging modalities and genetic testing improved

* Corresponding author. Tel: +49 89 4400 72300, Email: skaab@med.lmu.de
† The first two authors contributed equally to the study.
‡ The last two authors contributed equally as senior authors.
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Learning points

- The onset and progression of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) symptoms is typically coupled to physical exercise and may rest for years if the patient refrains from strenuous activity.
- The 2010 Task Force Criteria combined with 2019 HRS consensus statement offer guidance for ARVC/D diagnosis, if suspicion emerges from initial cardiologic assessment including medical case and family history, clinical presentation, electrocardiogram, and echocardiography.
- Right heart failure in ARVC/D patients can have a complex multifactorial aetiology including underlying fibro-adipose degeneration of ventricular myocardium, pulmonary arterial hypertension, intracardial (left-to-right) shunt, and secondary tricuspid regurgitation due to right ventricular (RV) dilation as well as implantable cardioverter-defibrillator lead interference, if implanted, requiring extensive haemodynamic diagnostics for optimal therapeutic management.
- Progressive exertional dyspnoea in ARVC/D patients may be significantly attributed to compromised left ventricular diastolic filling secondary to RV dysfunction.
- Follow-up appointments at a specialized multidisciplinary ARVC/D centre for continued symptomatic and instrumental re-assessment are key to tailor an individualized and sustained long-term management of this special patient cohort.

diagnoses, risk stratification, and prevention in high-risk groups.[9–12] Clinical management needs to be coordinated in a multidisciplinary approach in specialized ARVC centres with continuous re-evaluation based on disease progression.[4,13] The present case report focuses on the concomitant advent of symptoms and exercise, the importance of structured, guideline-aided diagnostic workup, and the role of haemodynamics in an optimized patient-tailored ARVC treatment strategy.

Timeline

1953	Year of birth
1970–1980	High-volume, moderate-intensity exercise (Class B, ∼4200 MET minutes weekly)
1978–1980	Recurrent exercise-induced palpitations—admission for 'atrial and ventricular irritability' without definite diagnosis
1980–2012	Symptom-free, low-volume weekend/holiday activity
2012–2020	Increased moderate-intensity exercise volume (Class B, ∼1800 MET minutes weekly), subtly progressing exertional dyspnoea and reduced exercise capacity
February–July 2020	Regular high-volume endurance sports after retirement, accelerating decline of exercise capacity and worsening symptoms
July–October 2020	Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) diagnosis with four major and one minor criterium (2010 Task Force Criteria)—heterozygous PKP-2 mutation in ARVC/D genetic panel Heart failure medication initiated with beta-blocker, angiotensin-converting enzyme-inhibitor, aldosterone antagonist Prophylactic implantable cardioverter-defibrillator implantation Monthly follow-ups
January 2021	Admission for worsening dyspnoea and physical limitation Comprehensive workup of tricuspid valve insufficiency aetiology and of right ventricular dilation and haemodynamics Escalation of medical therapy and replacement of bisoprolol for sotalol Monthly follow-ups
February 2021	Significant improvement regarding symptom burden, in particular a noticeably reduced dyspnoea and increased performance level, reduced ectopic burden, no further hospitalization

Case presentation

A 67-year-old male patient presented with dyspnoea and reduced cardiopulmonary exercise capacity. In his past medical history there was an admission for recurrent exercise-induced palpitations in 1980. At that time, he participated in high-frequency/high-duration/intermediate intensity endurance training (Class B, ∼4200 MET minutes/week). Subsequent cardiologic workup was not able to define underlying structural or rhythmical disease. A recommendation against exercise was not given, but coincidentally the patient ceased from his regular workouts in the early 1980s, when starting an ambitious career. His activity was confined to moderate-intensity training. In 2012, he restarted regular activity (Class B, ∼1800 MET minutes/week) and increased his workout volume in February 2020 when he retired. In July 2020, symptoms worsened significantly.

The patient presented with regular heart rate (HR), blood pressure (BP), and body mass index. Physical examination was noticeable for a 3/6-systolic murmur with punctum maximum at fourth intercostal space right parasternal. Key laboratory findings are presented in Supplementary material online, *Table S1*. His electrocardiogram (ECG) showed sinus rhythm with epsilon waves in V1–4 and T-wave inversions in leads II, III, aVF, and V1–6 (*Figure 1A*). Transthoracic echocardiography (TTE) showed enlarged and dyskinetic RV with aneurysmatic extension on RV free wall (RV end-diastolic diameter basal: 65 mm, tricuspid annular plane systolic excursion: 21 mm, RV outflow tract in parasternal long-axis view: 53 mm, RV outflow tract

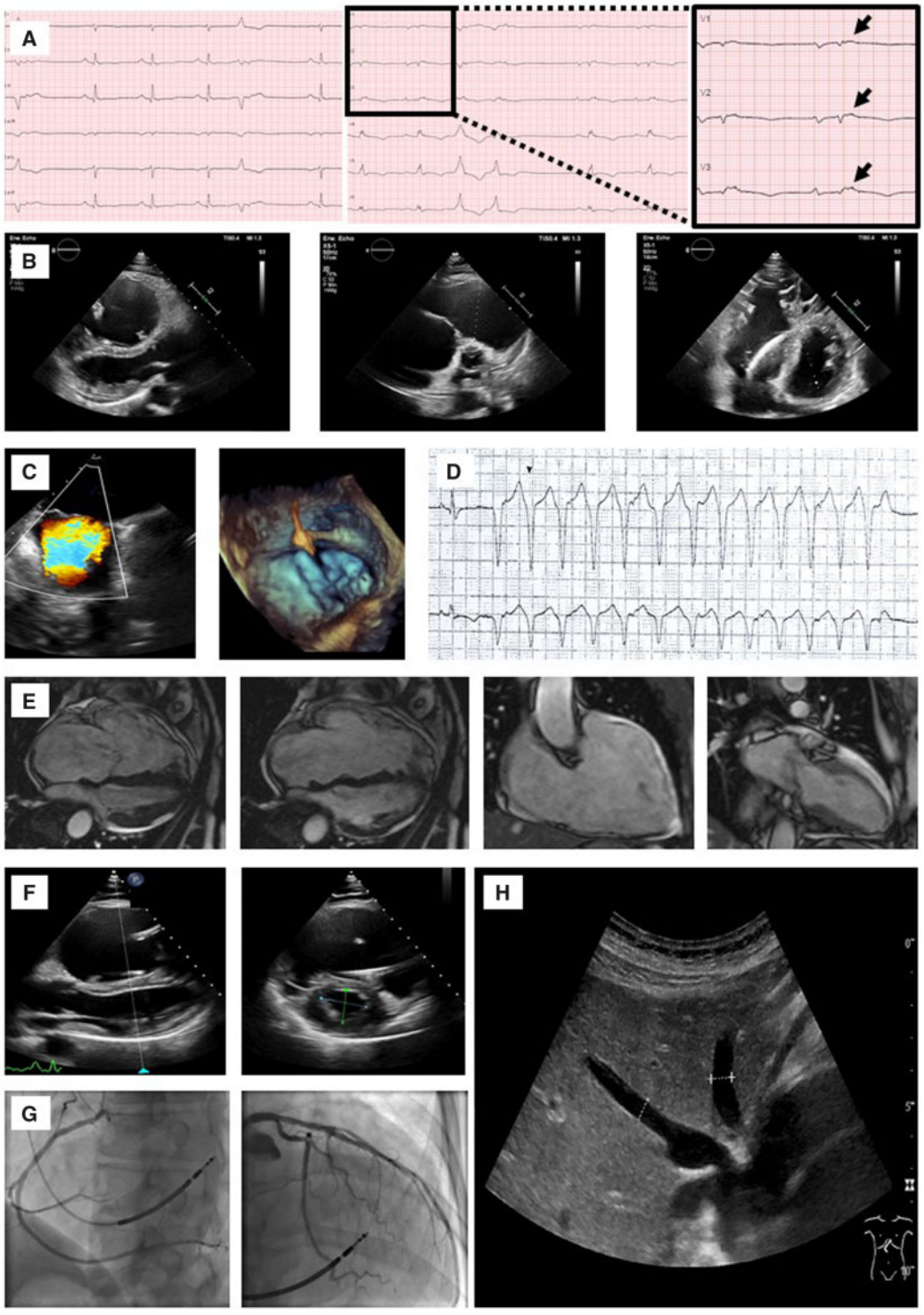


Figure 1 Diagnostic findings. (*A*) Resting electrocardiogram. (*B*) Resting transthoracic echocardiography with parasternal axis, parasternal short-axis, and apical four-chamber view (right ventricular end-diastolic diameter basal: 65 mm, tricuspid annular plane systolic excursion: 21 mm, right ventricular outflow tract in parasternal long-axis view: 53 mm, right ventricular outflow tract in parasternal short-axis view: 61 mm). (*C*) Transoesophageal echocardiogram showing severe tricuspid regurgitation in two-dimensional and three-dimensional (grade III/III, effective regurgitant orifice area: 53 mm^2, coaptation defect: 8–9 mm). (*D*) Non-sustained ventricular tachycardia documented on 24 h Holter electrocardiogram. (*E*) Cardiac magnetic resonance imaging showing tricuspid regurgitation in systole and diastole as well as sagittal axis of diastolic right ventricular and left ventricular size. (*F*) Stress transthoracic echocardiography showing secondary compromised left ventricular diastolic filling at 75 W. (*G*) Diagnostic angiogram showing coronary sclerosis without relevant obstructions. (*H*) Abdominal ultrasound illustrating systolic flow reversal in dilated liver vessels (up to 17 mm diameter) and inferior vena cava (28 mm diameter).

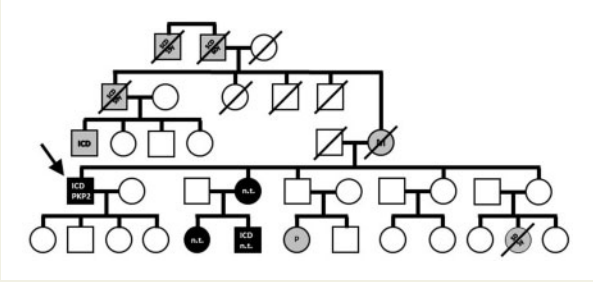
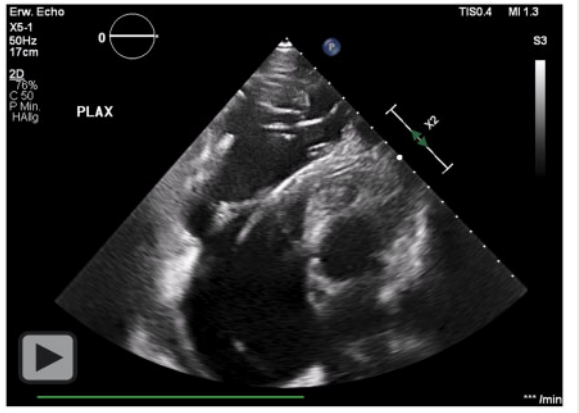


Figure 2 Family pedigree. *Circles* = females, *squares* = males, *arrow* = index patient, *oblique stroke through symbol* = dead, *blacked* = confirmed arrhythmogenic right ventricular cardiomyopathy/dysplasia, *grey* = symptomatic for unknown cause or other cardiac disease, *white* = unknown or without clinical signs of arrhythmogenic right ventricular cardiomyopathy/dysplasia or heart disease. ICD, implantable cardioverter-defibrillator; M, myocardial infarction; n.t., no genetic testing; P, heart palpitations; SCD, sudden cardiac death, SD, sudden death.



Video 1 Transthoracic echocardiogram with apical four chamber view focusing right heart.

in parasternal short-axis view: 61 mm), as well as high-grade tricuspid regurgitation (TR) (grade III/III, effective regurgitant orifice area: 53 mm^2, coaptation defect: 8–9 mm) and low-grade pulmonary regurgitation (grade I/III). Left ventricular (LV) size and function were preserved [LV ejection fraction (EF): 55%] and there were no relevant vitia of aortic and mitral valve (*Figure 1B and C and Video 1–3*).

We suspected RV cardiomyopathy and investigated patient's family history. Indeed, his sister had been diagnosed with ARVC as well as both of her teenage children, one of whom suffered from cardiac arrest while playing tennis at the age of 19 but was successfully resuscitated. His uncle, grandfather, and great-uncle sadly passed away from SCD at the age of 59, 60, and 19, respectively (*Figure 2*). In a synopsis of these initial findings, we initiated workup according to 2010 modified Task Force Criteria.[8]

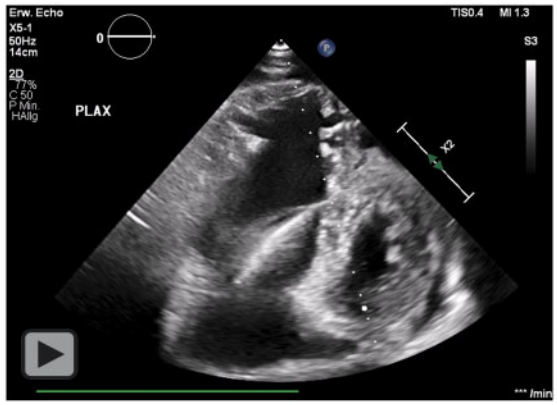
Seven-day Holter ECG showed two non-sustained ventricular tachycardias (maximum length of 12 beats) and an ectopic beat burden of 22 000/24 h (*Figure 1D*). Cardiac magnetic resonance imaging (MRI) correlated largely with echocardiographic findings: besides functional and morphological abnormalities, i.e. akinesia of the RV apical and medial anterior wall with signs of fatty degeneration, RV dilation and EF were further quantified (RV end-diastolic volume index: 227 mL/m^2, RVEF18%) (*Figure 1E*). Complementary genotyping revealed heterozygous nonsense substitution in PKP-2 gene (NM_004572.3: c.369G>A; p. Trp123Ter), which matched the ARVC phenotype in three databases for clinical variants (ClinVar, dbSNP, gnomAD) (*Table 1*).[14,15] Conclusively, ARVC was established as definite diagnosis (*Table 2*).[8]

Medical heart failure therapy including beta-blocker, angiotensin-converting enzyme-inhibitor, and aldosterone antagonist was introduced. Using the ARVC risk score,[16] the risk for a fast ventricular tachycardia/ventricular flutter/sustained ventricular arrhythmia was calculated at 7.1% within 5 years and patient underwent prophylactic implantable cardioverter-defibrillator (ICD) implantation. The latter was complicated by poor impedance levels at preferred implantation site in apical RV myocardium. Adequate connectivity was finally achieved after implantation into high-septal myocardium.

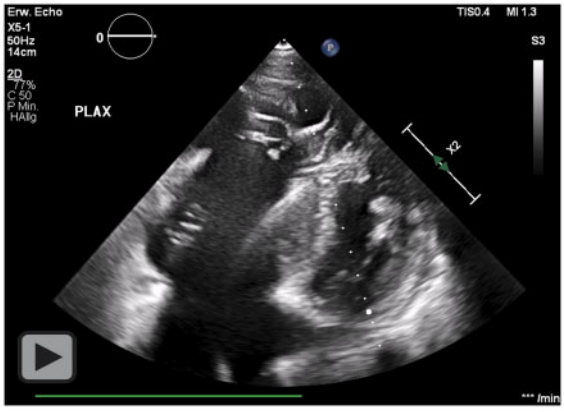
The patient was advised against smoking, high-cholesterol diet, exercise training, and anaerobic activity. We offered psychological counselling and consultation of a local ARVC support group. Monthly follow-ups were set in our specialized ARVC centre and mutation-specific cascade family testing was recommended in our cardiogenetic centre.

On regular follow-up 4 months later, the patient reports clinical deterioration. Electrocardiogram findings appeared unchanged. The ICD device did not elicit ventricular tachycardias. Repeated echocardiography showed severe TR (effective regurgitant orifice area: 40 mm^2, proximal isovelocity surface area: 7–8 mm), which now appeared to be additionally aggravated by interference of ICD lead with septal leaflet. Of note, echocardiography-controlled repositioning of the ICD lead did not seem to be promising considering the difficulties in ICD implantation and fragile nature of the RV myocardium. During exercise stress testing, systolic BP and HR increased appropriately. Furthermore, we performed stress echocardiography and supine incremental stepwise cycle exercise right heart catheterization to investigate resting and stress haemodynamics. The onset of dyspnoea at 75 W was correlated with diastolic LV compression and obstruction of LV filling by increasing RV pressure and RV failure (*Figure 1F*). Left ventricular early systolic volume at 100 W was estimated to 50 mL.

Diagnostic angiogram showed coronary sclerosis without obstructions (*Figure 1G*). Resting pulmonary artery (PA) systolic/diastolic and mean pressures were measured at 25/16 and 23 mmHg, respectively. Exercise-induced PA pressures rose slightly to 32/23 and 26 mmHg. The transpulmonary gradient remained regular at rest and when subjected to stress at 12 and 14 mmHg, respectively. Pulmonary artery oxygen saturation was 49% at rest and 37% at performance limit, evidencing slightly increased peripheral oxygen extraction. Overall, there was no evidence for pulmonary hypertension. Extended pulmonary diagnostics using high resolution computed tomography of lungs and spirometry excluded any obstructive and restrictive lung pathologies. Abdominal ultrasound documented systolic flow reversal in dilated liver vessels and inferior vena cava (*Figure 1H*). Gastrointestinal symptoms and dilated liver veins were interpreted as progressing signs of right heart congestion with beginning



Video 2 Transthoracic echocardiogram with apical four chamber view focusing right heart.



Video 3 Transthoracic echocardiogram with apical four chamber view focusing right heart.

congestive gastritis and hepatopathy (AST 59 U/L, ALT 73 U/L, GGT 149 U/L, bilirubin 0.9 mg/dL).[17]

We expanded medical treatment by adding standard coronary artery disease prophylactic agents, namely acetylsalicylic acid and rosuvastatin. Heart failure medication was modified by adding torasemide and antiarrhythmic medication was adjusted by discontinuation of bisoprolol in favour of sotalol (*Table 3*). Despite conflicting evidence, sotalol is still a guideline-recommended prophylactic agent for patients with ARVC/D, which is based on data from the OPTIC study, showing a trend towards fewer ICD shocks in patients treated with sotalol compared to beta-blockers.[18] On the next regular follow-up, the patient reported a significant improvement regarding symptom burden. Thus, therapy was continued in its present form with regular re-assessments in ongoing monthly follow-ups.

Discussion

Symptomatic arrhythmias and SCD are characteristic clinical manifestations of ARVC/D in early adulthood. When our patient first experienced ventricular tachycardias in 1980, the first identification of a genotype in 2000 was still years away.[19] The abstinence from sports after what in hindsight appears to be a typical manifestation of ARVC/D may have been protective but also delayed diagnosis until the threshold age for heart transplant had already passed. The presented course of disease highlights the liaison of exercise with the onset of symptoms even after a 'concealed phase'.[8]

The onset of ARVC/D symptoms can be non-specific, which poses major challenges. Awareness of red flags and accurate interpretation of initial findings are pivotal for launching diagnostic workup. The landscape of available imaging tools and genetic sequencing has improved, allowing for a disclosure of all Task Force Criteria and an array of the most common underlying mutations in desmosomal/non-desmosomal genes (*Table 1*).[20] In this case, ARVC/D as leading differential diagnosis was already verified by family history (major criterium), ECG (major criterium), and echocardiogram (major criterium) (*Table 2*). The following 24 h ECG (minor criterium), MRI (major criterium), and genetic findings (major criterium) not only solidified the initial suspicion, but also refined the understanding of underlying pathophysiological processes and morphological features to adequately estimate the risk of malignant arrhythmias and SCD, evaluate medical, interventional, and surgical treatment options, and offer mutation-specific cascade screening in all first-degree relatives.

Extended workups including haemodynamics in specialized ARVC/D centres should be aspired even after straightforward ARVC/D diagnosis. High-grade TR may be contingent solely on RV dilation but complicated by atypical ICD positioning.[21] Accessory pathologies, like pulmonary hypertension or intracardial left-to-right shunt, are also difficult to separate from ARVC/D-originated right heart failure, but potentially offer treatment options.[22,23] Progressing dyspnoea may in cases like this justify a more comprehensive/invasive evaluation of haemodynamics by stress echocardiography and right heart catheterization. In absence of relevant pulmonary hypertension and intracardiac shunt, the results of those offered a coherent explanation for his physical limitation: compromised LV diastolic filling due

Table 1 Arrhythmogenic right ventricular cardiomyopathy next-generation sequencing panel according to the HRS/EHRA expert consensus statement on the state of genetic testing for channelopathies and cardiomyopathies[14,15]

Tested gene	Detected mutation
Desmocollin-2 (DSC2)	Not detected
Desmoglein-2 (DSG2)	Not detected
Desmoplakin (DSP)	Not detected
Plakoglobin (JUP)	Not detected
Plakophilin-2 (PKP2)	NM_004572.3:c.369G>A (p.Trp123Ter)
Desmin (DES)	Not detected
Transmembrane protein 43 (TMEM43)	Not detected
Transforming growth factor ß3 (TGFB3)	Not detected
Ryanodine-Receptor (RYR2)	Not detected

Table 2 2010 modified arrhythmogenic right ventricular cardiomyopathy/dysplasia diagnostic Task Force Criteria[8]

Category	Findings	Valuation
(I) Global or regional dysfunction and structural alterations	*2D echocardiography:* Regional RV dyskinesia and PLAX RVOT 53 mm/PSAX RVOT 61 mm *Cardiac MRI:* RV dyskinesia and RV EDVI 227 mL/m^2/RVEF 18%	Major criterion
(II) Tissue characterization of wall	—	—
(III) Repolarization abnormalities	T-wave-inversions in leads V1, V2, and V3	Major criterion
(IV) Depolarization/conduction abnormalities	Epsilon wave in leads V1, V2, and V3	Major criterion
(V) Arrhythmias	22 000 ventricular extrasystoles/24 h	Minor criterion
(VI) Family history	ARVC/D confirmed in one sister	Major criterion

2D, two-dimensional; ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; EDVI, end-diastolic volume index; MRI, magnetic resonance imaging; RVEF, right ventricular ejection fraction; RVOT, right ventricular outflow tract.

Table 3 Medication at discharge

Compound	Dosage (mg p.o.)	Drug intake schedule
Acetylsalicylic acid	100	1–0–0
Sotalol	120	1–1/2–1
Ramipril	1.25	1–0–0
Eplerenone	25	1–0–0
Torasemide	5	1–0–0
Rosuvastatin	20	0–0–1
Pantoprazol	40	1–0–0

p.o., per os.

to exercise-exacerbated right heart failure and increased RV pressure, resulting in a compromised global circulation.

We first introduced standard pharmacologic therapy and provided adequate risk-based arrhythmia protection by ICD implantation. Atypical positioning is not uncommon in ARVC/D patients, which may worsen pre-existing TR and contribute to deterioration. In this regard, transoesophageal echocardiography-controlled repositioning of ICD lead may be considered.[24] Additionally, interventional approaches like tricuspid valve edge-to-edge repair may be considered. However, more evidence regarding therapeutic salvage strategies is needed. In the present case, we decided in favour of an optimized medical treatment approach. Considering, that regular follow-ups in an ARVC/D centre are a crucial part of sustained long-term care. In pursuit of a holistic treatment concept, our patient and his family were also referred to our psychological, sports cardiological, and genetic specialists.

Conclusion

This case report emphasizes the diversity of ARVC/D manifestations and the challenges of its recognition and diagnosis. The 2010 Task Force Criteria together with the 2019 HRS consensus statement offer a pathway for ARVC/D detection and individual phenotypic characterization. In some patients, aetiology of symptoms may be inconclusive, requiring extensive imaging and invasive diagnostic workup to tailor medical, surgical, and interventional treatment options for optimal symptom control and arrhythmia prophylaxis. Finally, the psychological implications of ARVC/D diagnosis on index patients and their families should not be underestimated and therefore be considered as part of long-term follow-up in specialized centres.

Lead author biography

Enzo Lüsebrink graduated in economics from the University of Mannheim and received a doctor's degree at the University of Mannheim. He achieved his licence to practice medicine at the University of Bonn with internships at the University Hospitals of Bonn, Berlin, Hamburg, Heidelberg, and Munich. He finished his medical doctoral thesis at the University of Bonn. At present, he is a resident physician for cardiology and internal medicine at the University Hospital of the Ludwig-Maximilians University Munich and is working in the cardiac intensive care unit.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

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

Conflict of interest: M.O. received speaker honoraria from Abbott Medical, AstraZeneca, Abiomed, Bayer vital, BIOTRONIK, Bristol-Myers Squibb, CytoSorbents, Daiichi Sankyo Deutschland, Edwards Lifesciences Services, and Sedana Medical, outside the submitted work. All other authors declared no conflict of interest.

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