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Case Report: Arrhythmogenic Right Ventricular Dysplasia

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Abstract

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic disorder that increases risk of sudden cardiac death in young people. Its pathophysiology primarily involves fibro-fatty infiltration of the myocardium and subsequent cardiomyopathy and arrythmias. There are some interesting EKG findings associated with ARVC. Exact incidence is unknown but estimated to be between 1/2000-1/5000.

We present a 25-year-old female with significant family history of AVRC, who presented with palpitations. We discuss her initial EKG findings of T wave changes in Right precordial leads. Subsequent 2D Echo showed global biventricular dysfunction and reduced EF. She was started on GDMT for non-ischemic cardiomyopathy. MRI showed classic findings of ARVC, and the patient underwent genetic testing which was positive. Her subsequent clinical course and outpatient follow up with Cardiology specialists are discussed. We also go into a brief review of pathophysiology and classic EKG findings of ARVC.

Early recognition of this underrecognized pathology can lead to better outcomes with early ICD placement and pharmacological therapy.

Keywords: Arrhythmogenic, ARVC, EKG, Cardiomyopathy

Introduction

Arrhythmogenic right ventricular dysplasia (ARVD) also known as arrhythmogenic right ventricular cardiomyopathy (ARVC) is a hereditary disease of the myocardium. The right ventricular free wall's fatty infiltration is the cause of ARVC/D. This is a genetic disorder that may result in sudden mortality in young people and sportsmen. Guy Fontaine first recognized it in 1977. The onset of ventricular tachycardia with a pattern of left bundle branch block is a crucial aspect of this condition. It often manifests when exercising [1]. By identifying this illness and taking preventative measures, it is possible to save the lives of those who already have it. To identify those who are at risk, genetic testing in their family is crucial.

The normal inheritance pattern for arrhythmogenic right ventricular cardiomyopathy is autosomal dominant, with variable penetrance and partial manifestation. A mutation in a gene that codes for a desmosome protein is present in 40% to 50% of ARVC/D patients. The Naxos illness autosomal recessive trait variation is linked to palmoplantar keratosis and woolly hair, and it is located on chromosome 14q23-q24 [2].

The four phases of ARVC include the subclinical stage, which has concealed structural and functional problems; nonetheless, sudden cardiac death (SCD) may happen in this stage as well. Right ventricular (RV) arrhythmias and structural and functional abnormalities are overt ECG findings in the second stage. The third stage is characterized by significant right ventricular dysfunction without involvement of the left ventricle (LV). The fourth stage is characterized by substantial right and left ventricle dysfunction with biventricular involvement [3]. Being a rare condition, ARVC may be difficult to detect and diagnose, which can also cause a delay in treatment. Our case report highlights the conventional, clinical, and diagnostic ARVC results and addresses treatment options.

The use of antiarrhythmic drugs and an implanted cardioverter-defibrillator is customized and focused on preventing syncope, cardiac arrest, and sudden death [4]. Although severe diffuse biventricular involvement imitating dilated cardiomyopathy and needing heart transplantation seems to be unusual, it is taken into consideration when ARVC has advanced to right or left ventricular heart failure.

Case Presentation

25-year-old female with significant family history of cardiomyopathy in her mother, mother's fraternal twin and an uncle who passed away from sudden cardiac death at an early age.

At the age of 23, she started experiencing frequent palpitations, shortness of breath on exertion and mild lower extremity edema. As the patient works in the healthcare industry, she hooked herself to an EKG machine which showed frequent PVCs. she was then recommended to a cardiologist, who ordered an EKG (Fig 1, which showed small QRS complexes with T-wave inversion due to repolarization irregularities mainly in lead V1-V2, which can occur in ARVD), extended Holter monitor and 2D echo.

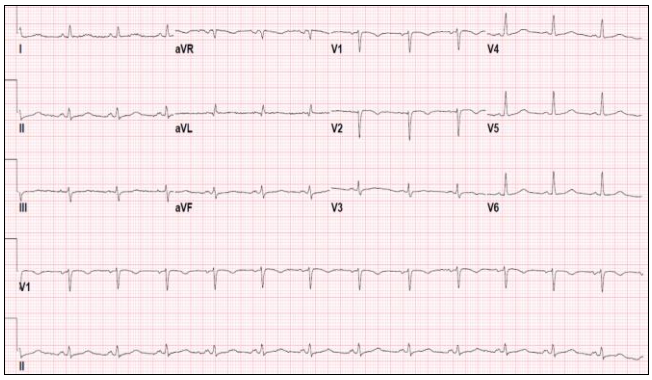

Fig 1: Initial EKG of the patient

Echo showed EF 37%, moderately reduced LV systolic function, global LV hypokinesis, LV global longitudinal strain 11%, grade 1 diastolic dysfunction and mildly reduced RV systolic function, with tricuspid annular plane systolic excursion (TAPSE) measured at 14(<17mm Hg positive for global RV dysfunction). Holter monitor showed multiple beats of Non sustained V-tach, longest of which was 6 beats. She was subsequently started on GDMT- Carvedilol 3.125 and lisinopril 2.5 and cardiac MRI was ordered for further evaluation. She was also referred to Electrophysiology due to episodes of non-sustained VTach.

MRI (Fig 2-3) correlated with 2D echo findings and in addition also showed extensive late gadolinium enhancement involving the mid and RV side of the interventricular septum from the base to the apex as well as subepicardial enhancement of the left ventricle (all segments). LVEF- 38%, RVEF 45%.

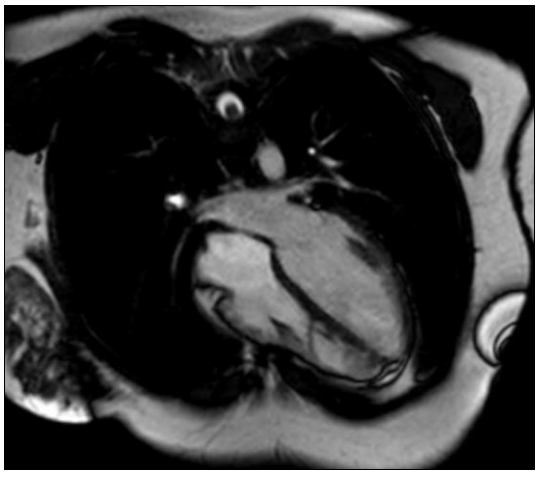

Fig 2: The patient's Cardiac MRI, showing features of ARVD

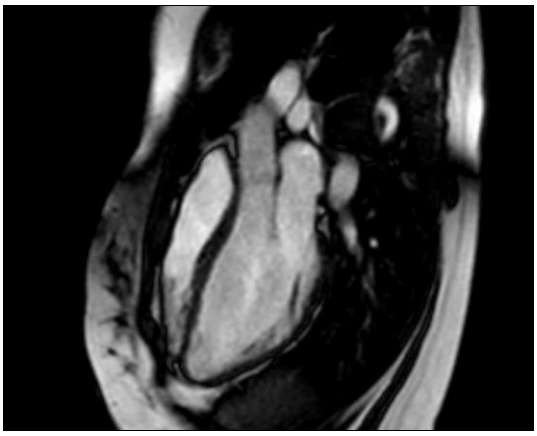

Fig 3: The patient's Cardiac MRI, showing features of ARVD

She followed up with her Cardiologist with the MRI results. She was switched to Metoprolol Succinate due to side effects of Carvedilol. She was also started on Spironolactone 25 and referred to a geneticist to discuss testing for cardiomyopathy. Workup for non-ischemic etiologies of cardiomyopathy including TSH, ferritin, TIBC, HIV screening, ANA antibody, viral serologies, Anti myosin antibody, ACE level, thiamine, carnitine, selenium levels; 24-hour urinary fractionated catecholamines and metanephrines; 24-hour urine protein electrophoresis, creatinine, estimated glomerular filtration rate, and serum albumin were ordered. The lab tests returned benign. 2-3 months after starting GDMT for HFrEF, patient started experiencing improvement of symptoms. Repeat Echo showed improvement in Heart function with LVEF 50%. Normal LV GLS of 19.0%. (Improved from prior strain of 11%). A repeat Event monitor was done which showed improvement in burden of Vtach and PVC episodes. She also underwent ischemic workup with negative CTA showing no epicardial coronary disease.

Around the same time of her presentation, patient's mother underwent genetic testing and was found to carry Gene: DSP, Mode of Inheritance: autosomal dominant, Variant: c.2275delG p.V759LfsX6, Zygosity: heterozygous, Classification: likely pathogenic variant, Chromosome: 6, Position 7574463. A likely pathogenic mutation in the desmoplakin gene. Pathogenic variants in the DSP gene are associated with autosomal dominant arrhythmogenic right ventricular cardiomyopathy and autosomal dominant dilated cardiomyopathy.

The patient did not perform genetic testing initially due to cost.

EP Cardiology were suspecting an inheritable arrhythmogenic cardiomyopathy and agreed with pursuing ICD placement with possible EP study after genetic testing was done. Patient was instructed to avoid endurance and competitive sports. Given these findings, DSP c.2275delG (p.V759LfsX6) targeted mutation-specific genetic testing was ordered by Pediatric Cardiology Genetics specialist after insurance approval. Her tests came back positive for the same gene as her mother. She subsequently underwent ICD placement for primary prevention of SCD. Currently she is doing better, at NYHA class 2, euvolemic, most recent EF of 45%. She also follows up with an Advanced Heart Failure team who transitioned her to Entresto(ARB/ARNI). She will have annual Echos to serially monitor her heart function in the future.

Discussion

ARVC, a progressive inherited cardiomyopathy with an increased risk of ventricular arrhythmias and abrupt cardiac death, was first described by Dr. Frank Marcus in 1982. (SCD). Histologically, the RV myocardium is replaced by fibro-fatty tissue, which leads to RV dilatation and systolic failure [1]. Contrary to its name, ARVC may affect the left ventricle and result in left-sided heart failure. A 1:2000–1:5000 prevalence estimate has been made. It is believed that the mutation of multiple genes encoding desmosomes, which are in charge of cell-to-cell adhesion, underlies disease [5]. Myocyte detachment and cell death, as well as ongoing mechanical stress or myocardial contraction, are all caused by malfunctioning desmosomes. This process causes the afflicted myocardium to experience an initial period of inflammation, followed by apoptosis and the replacement of the myocardium by fibro-fatty tissue. Macro-reentrant ventricular tachycardia (VT), on the other hand, is linked to fibrofatty scarring in ARVC, while ventricular fibrillation (VF) may develop during the process of cell death. In autosomal dominant ARVC, mutations of non-desmosomal genes have also been documented.

However, some people may exhibit symptoms including palpitations, lightheadedness, cardiogenic syncope, heart failure, ventricular arrhythmias, or cardiac arrest. Many patients may continue to be asymptomatic. Epsilon waves in the right precordial leads and symmetrically inverted T waves are reported EKG abnormalities in around 30% of ARVC patients (V1, V2 and V3). Epsilon waves are characterized as low-amplitude positive signals at the conclusion of QRS complexes and are thought to be caused by slower depolarization of the afflicted region of the RV myocardium. The most prevalent ventricular arrhythmia linked with ARVC is monomorphic VT with LBBB pattern. [4, 5] Additionally, supraventricular arrhythmias have been documented. Progressive heart failure and SCD are to blame for cardiovascular death in ARVC patients in that order of frequency. Those who have a history of ventricular tachycardia are more at risk for SCD [6]. The phenotypic penetrance varies and is closely correlated with exercise frequency.

According to James *et al*., the intensity of endurance activity has an effect on the disease's phenotypic penetrance and the development of VT and SCD in athletes [7]. NSVT may appear on a Holter monitor in a variety of morphologies. ECHO may reveal lower RV EF, increased RV dimension (particularly at the RV outflow tract), and regional abnormalities in RV wall motion. The diagnosis of ARVC with relatively good sensitivity and specificity has been made possible by developing technologies, however inter-observer variability has been noted [8]. To search for inducible VT, EPS might be used as a diagnostic tool. Electroanatomic mapping may also be used to determine the disease's severity [9]. EPS may also be used to direct an endomyocardial biopsy. However, owing to patchy myocardial involvement and poor sensitivity from sample mistakes, the utility of endomyocardial biopsy (EMB) remains debatable. On the other hand, when the diagnosis of ARVC is indeterminate and when focused genetic screening of first-degree relatives is intended, genetic testing may be beneficial. As a first step to make the diagnosis, neither EMB nor genetic testing are advised.

According to the literature, 50% of ARVC patients are familial, albeit this number may be understated. Both the autosomal dominant and autosomal recessive forms of the illness may be inherited, with the former being more prevalent. There have been reports of many genes in the autosomal dominant illness. One of these is the most prevalent mutation found in North America, the plakophilin-2 gene (PKP-2), which encodes the desmosomal protein plakophilin-2 [10]. With a mean beginning age of 28 (11 years), patients with PKP-2 mutations tend to experience symptoms and arrhythmias sooner in life.

The pathophysiology of arrhythmogenic right ventricular cardiomyopathy/dysplasia is uncertain. Pathogenesis seems to involve apoptosis. The endocardial surface is first affected by the disease process, which then spreads to the subepicardial region and causes transmural involvement. In 50% of cases, aneurysmal dilatation is evident. The triangle of dysplasia, which includes the diaphragm, apical region, and infundibulum, is where an aneurysm develops. 50% to 67% of cases involve the left ventricle [11]. The left ventricle's involvement indicates a dismal prognosis. Both fatty infiltration and fibro-fatty infiltration are pathological features associated with ARVC/D (Fig 4).

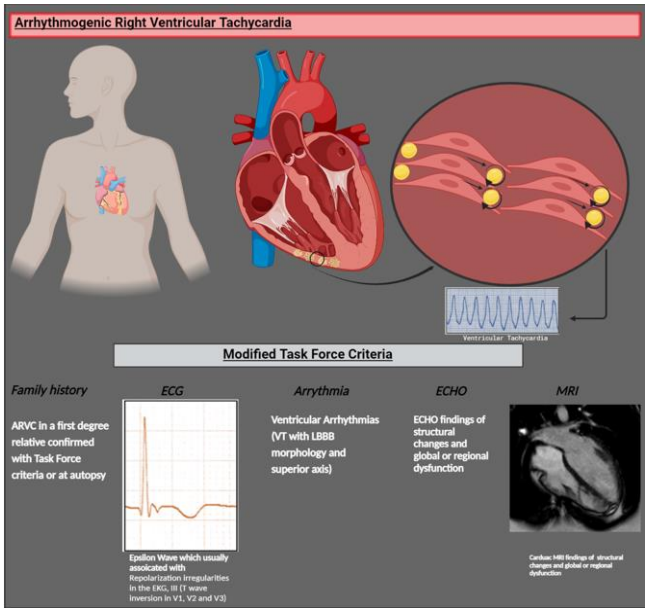

Fig 4: Clinical Illustration of Arrhythmogenic Right Ventricular dysplasia

A progressive condition is ARVC/D. Over time, the right ventricle gets increasingly engaged, eventually failing. By the time the person has right ventricular failure, histologic alterations in the left ventricle might have already occurred. Biventricular failure eventually results from the development of left ventricular failure [12]. Congestive heart failure, atrial fibrillation, and thromboembolic events are subsequent stages of the illness.

Typically, autosomal dominant inheritance is used to pass down ARVC. A de novo pathogenic mutation may cause the condition in a proband with autosomal dominant ARVC. Unknown is the percentage of instances brought on by a de novo variation. A parent with autosomal dominant ARVC has a 50% probability of passing the pathogenic mutation to each of their children [11]. Additionally, digenic inheritance of ARVC is possible (i.e., a single allele of two different genes has a pathogenic variant). If the pathogenic variant(s) have been found in the family, prenatal diagnosis for pregnancies at higher risk is achievable.

It might be difficult and very vital to make the right diagnosis. The 2010 updated Force Criteria, which are divided into the following six categories, were suggested by Marcus *et al* [13].

1. CMRI or ECHO structural changes and global or regional dysfunction
2. Wall tissue characterisation (fibrous replacement and percentage of residual myocytes in right ventricle)
3. Repolarization irregularities in the EKG, III (T wave inversion in V1, V2 and V3)
4. Abnormalities of depolarization and conduction on the EKG (epsilon wave in V1, V2 and V3)
5. Arrhythmias (VT with LBBB morphology and superior axis)
6. Family background (ARVC in a first degree relative confirmed with Task Force criteria or at autopsy)

Each of the six categories is further broken into major and minor requirements. Diagnoses are confirmed as follows:

- Borderline diagnosis with one major and one minor or three minor criteria from separate categories;
- Definite diagnosis with two major, one major and two minor, or four minor criteria;
- Potential diagnosis based on one or two minor characteristics from several categories.

Given the significant correlation between the prevalence of ventricular arrhythmias and endurance activity, lifestyle change is advised for all patients with ARVC. Patients with ARVC should refrain from participating in any competitive sports as well as any physical activity that results in palpitations or pre-syncope [7, 10]. Exercise accelerates the course of the illness, necessitating the prescription of -blockers for sympathetic suppression and possible improvements in clinical results. However, there isn't enough solid proof to back up the empiric usage of -blockers. Inhibitors of the angiotensin-converting enzyme may also slow the disease's structural development and shield the heart against arrhythmias [14]. Patients with ARVC who develop heart failure should get conventional medical care.

In families where the pathogenic variation is known, at-risk relatives should undergo molecular genetic testing; individuals who have the familial pathogenic variant should undergo yearly clinical cardiac function and rhythm checks between the ages of 10 and 50 [15]. A clinical screening for cardiac involvement is advised for asymptomatic at-risk first-degree relatives beyond the age of ten if genetic testing has not been done or did not reveal a pathogenic mutation in an afflicted family member.

ICD treatment may also aid in the management of ventricular arrhythmias and the prevention of SCD. According to the agreement of experts, ICD treatment is recommended for secondary prevention in people who have a history of persistent VT or aborted cardiac arrest as well as for primary prevention in those who are at high risk [16]. However, neither the specific criteria for ICD implantation among ARVC patients nor agreement on how to categorize the high-risk individuals have been thoroughly established. However, randomized control studies have shown that ICD treatment is effective in reducing the risk of SCD in those who are at high risk. Prospective research reports the successful anti-tachycardia pacing (ATP) termination of ventricular tachyarrhythmias in ARVC patients [17]. ICD treatments come with hazards of pericardial effusion, perforation, device infection, and incorrect shocks, just as in other situations with proper installation. Due to thin portions of the RV myocardium and growing fibro-fatty infiltration, respectively, myocardial perforation and under-sensing of arrhythmias are of particular concern in ARVC.

Ventricular arrhythmia incidence may be decreased by the use of anti-arrhythmic medications, often sotalol. Anti-arrhythmic drugs are not a substitute for ICD treatment; rather, they are utilized as an adjuvant therapy in ARVC patients with ICD devices. In addition, specialists advise using sotalol or amiodarone in ARVC patients who are unable to tolerate ICD medication [16]. Radiofrequency ablation cannot be regarded as a curative treatment due to the myocardium's patchy involvement. End-stage heart failure and refractory ventricular arrhythmias are treated with surgery and heart transplantation, respectively. An ICD was implanted as a main preventive treatment in our patient because to the clinical symptoms of palpitation, fibrofatty alterations in the RV myocardium, and inducible VT in EPS [18]. The correct utilization of medical resources, such a cardiac MRI, is also shown in this instance, which at first presented a diagnostic issue.

Despite the fact that all ARVC patients have a slightly elevated risk of having ventricular tachyarrhythmias and heart failure, many people generally perform well. Due to age-related phenotypic penetrance, asymptomatic family members of an afflicted patient may get ARVC later in life. Given that individuals with inducible persistent monomorphic VT have a greater risk of SCD, EPS may be useful in risk-stratification [12]. According to the literature, ARVC has a better overall prognosis than other structural heart illnesses that result in ventricular-originated arrhythmias.

Conclusion

A genetic cardiomyopathy called ARVC carries an increased risk of SCD and ventricular arrhythmias. It is an uncommon condition; thus, a proper diagnosis is crucial to avoiding needless delays in the patient's care. All components to diagnose ARVC are included in the updated task force guidelines released in 2010. Since SCD is the most dreaded ARVC consequence, early identification and insertion of an ICD might save lives. As a result, it is crucial to understand the potential ARVC EKG results and to understand whether to do more research and apply medications.

References

1. Nunes J, De Alencar Neto A, Baranchuk A, Bayés-Genís A, Bayés De Luna. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: An electrocardiogram-based review, EP Eur. 2018; 20(FI1):f3-f12. Doi: 10.1093/EUROPACE/EUX202
2. Gandjbakhch E, Redheuil A, Pousset F, Charron P, Frank R. Clinical Diagnosis, Imaging, and Genetics of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: JACC State-of-the-Art Review, J. Am. Coll. Cardiol. 2018; 72(7):784-804. Aug. Doi: 10.1016/J.JACC.2018.05.065
3. Bhonsale A, *et al*. Cardiac phenotype and long-term prognosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia patients with late presentation, Hear. Rhythm. 2017; 14(6):883-891. Doi: 10.1016/J.HRTHM.2017.02.013

4. Orgeron GM. *et al.* Implantable cardioverter-defibrillator therapy in arrhythmogenic right ventricular dysplasia/cardiomyopathy: Predictors of appropriate therapy, outcomes, and complications, J. Am. Heart Assoc. 2017; 6(6). Doi: 10.1161/JAHA.117.006242
5. Calkins H. Arrhythmogenic right ventricular dysplasia/cardiomyopathy-Three decades of progress, Circ. J. 2015; 79(5):901-913. Doi: 10.1253/CIRCJ.CJ-15-0288
6. Corrado D, Zorzi A. Arrhythmogenic right ventricular cardiomyopathy and sports activity, Eur. Heart J. 2015; 36(27):1708-1710. Doi: 10.1093/EURHEARTJ/EHV183
7. Kori AMM, Lim WK, Mokhtar SAI. Arrythmogenic right ventricular dysplasia, Med. J. Malaysia. 2016; 71(6):357-359. Doi: 10.1161/CIRCULATIONAHA.105.542266
8. Wang W, James CA, Calkins H. Diagnostic and therapeutic strategies for arrhythmogenic right ventricular dysplasia/cardiomyopathy patient, EP Eur. 2019; 21(1):9-21. Doi: 10.1093/EUROPACE/EUY063
9. Te Riele ASJM, *et al*. Approach to family screening in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Eur. Heart J. 2016; 37(9):755-763. Doi: 10.1093/EURHEARTJ/EHV387
10. James CA, Calkins H. Arrhythmogenic right ventricular cardiomyopathy: Progress toward personalized management, Annu. Rev. Med. 2019; 70:1-18. Doi: 10.1146/ANNUREV-MED-041217-010932
11. Saffitz JE. The pathobiology of arrhythmogenic cardiomyopathy, Annu. Rev. Pathol. Mech. Dis. 2011; 6:299-321. Doi: 10.1146/ANNUREV-PATHOL-011110-130151
12. Sen-Chowdhry S, Morgan RD, Chambers JC, McKenna WJ. Arrhythmogenic cardiomyopathy: Etiology, diagnosis, and treatment, Annu. Rev. Med. 2010; 61:233-253. Doi: 10.1146/ANNUREV.MED.052208.130419
13. Fontaine G. *et al*. Arrhythmogenic Right Ventricular Dysplasia. 2003; 50:17-35. Doi: https://doi.org/10.1146/annurev.med.50.1.17 Doi: 10.1146/ANNUREV.MED.50.1.17
14. Qadri S. *et al*. Case reports of two pedigrees with recessive arrhythmogenic right ventricular cardiomyopathy associated with homozygous Thr335Ala variant in DSG2," BMC Med. Genet. 2017; 18(1):1-9. Doi: 10.1186/S12881-017-0442-3/FIGURES/3
15. Mu J, Zhang G, Xue D, Xi M, Qi J, Dong H. Sudden cardiac death owing to arrhythmogenic right ventricular cardiomyopathy: Two case reports and systematic literature review, Medicine (Baltimore). 2017; 96(47). Doi: 10.1097/MD.0000000000008808
16. Claus P, Omar AMS, Pedrizzetti G, Sengupta PP, Nagel E. Tissue tracking Technology for Assessing Cardiac Mechanics: Principles, normal values, and clinical applications, JACC Cardiovasc Imaging. 2015; 8(12):1444-1460. Doi: 10.1016/j.jcmg.2015.11.001
17. Pedrizzetti G, Claus P, Kilner PJ, Nagel E. Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use, J Cardiovasc Magn Reson. 2016; 18(1):51. Doi: 10.1186/s12968-016-0269-7
18. Bourfiss M. *et al*. Feature tracking CMR reveals abnormal strain in preclinical arrhythmogenic right ventricular dysplasia/ cardiomyopathy: A multisoftware feasibility and clinical implementation study, J. Cardiovasc. Magn. Reson. 2017; 19(1):1-13. Doi: 10.1186/S12968-017-0380-4/TABLES/4