Arrhytmogenic Right Ventricular Dysplasia/ Cardiomyopathy (ARVD/C) and Heart Transplantation: Case Series

Aritmojenik Sağ Ventrikül Displazisi/Kardiyomiyopati (ARVD/C) ve Kalp Nakli: Olgu Serileri

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ABSTRACT Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) usually originates from right ventricle, has a prevalence 1 in 1000 and leading cause of death in people aged less than 35 years of age, also desmosome mutations and family history can be seen in this disease. We reviewed the literature and described three patients with arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVD/C). They had T wave inversion in chest leads V1 to V4 and had premature ventricular complexes of left bundle branch block and left axis deviation, or right bundle branch block (RBB) had implantable cardioverter defibrillator (ICD) implantation and fulfilled the task force criteria for diagnosis of ARVD/C. One patient had familial erythrocytosis and thrombus formation in the right atrium and the right ventricle. He was listed as status 1A and had 2 times phlebotomy during the hospitalization. The other patient had warfarin intoxication, and had hepatic congestion due to end-stage right heart failure. The third patient had a history of cerebrovascular event and had a family history of ARVD/C. All of our patients had the medical regimen for the management of ARVD/C. All of the patients were in NYHA Class III-IV while they admitted to our clinic and they had their final therapeutic option as an orthotopic heart transplantation and have a good quality of life.

Key Words: Arrhythmogenic right ventricular dysplasia; heart transplantation

ÖZET Aritmojenik sağ ventriküler displazisi/kardiyomiyopati (ARVD/C), sağ ventrikülden orijin alır, 1000'de 1 görülme sıklığı vardır, 35 yaşından genç insanlarda en fazla ölüm sebeplerindendir. Bu hastalıkta desmozom mutasyonları ve aile hikayesi görülebilir. Biz detaylı olarak literatürü taradıktan sonra, aritmojenik sağ ventrikül displazisi/kardiyomiyopati (ARVD/C) olan 3 hastamızı sunuyoruz.V1'den V4'e kadar tüm göğüs derivasyonlarında ve sol dal bloğu ile prematür ventrikül atımlar ve sol aks deviasyonu ve sağ dal bloğu tespit edilmesi üzerine hastalara kardiyoverter implantable defibrilatör (ICD) implante edildi. Hastalarımızdan biri 1A statüsünde idi ve hastanede bulunduğu sürede 2 kez filebotomi yapıldı. Diğer hastanın warfarin intoksikasyonu ve sağ kalp yetmezliğine bağlı karaciğer konjesyonu mevcuttu. Üçüncü hastamızın da daha önce geçirilmiş serebrovasküler olayı ve ARVD/C aile hikayesi vardı. Tüm hastalarımız ARVD/C yönelik maksimum medikal tedavilerini almışlardı ve kliniğimize başvurduklarında New York Heart Association (NYHA) Klass III-IV idiler ve onlar için en iyi tedavi kalp nakli olmaları idi. Ortotopik kalp naklini olduktan sonra daha iyi bir yaşam kaliteleri oldu.

Anahtar Kelimeler: Aritmojenik sağ ventriküler displazi; kalp nakli

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Arrhytmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a heart muscle disease of unknown etiology, characterized by peculiar right ventricular (RV) involvement, has a prevalence of at least 1 in 1000 and ventricular arrhythmias, sudden death may be observed.[1]

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The symptoms may occur with ventricular tachycardias (VT) with a left bundle branch block (LBBB) or ventricular fibrillation (VF) causing sudden cardiac arrest mostly in young people between 20 to 40 years of age. As the disease progress, right ventricular muscle disease may cause left ventricular involvement which result in biventricular heart failure.[2]

Clinical diagnosis of ARVD/C may be difficult, in 1994 the study group on ARVD/C of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the World Heart Federation reported the guidelines for clinical diagnosis.[3] The 1994 criteria focused on the right ventricular (RV) disease manifestations depending on the minor and major criteria for global or regional dysfunction and structural alterations, tissue characterization of the wall, repolarization-depolarization abnormalities, arrhythmias and family history. Over the past 15 years additional markers of the disease have been proposed and newer imaging technologies have been introduced, and also genotype-phenotype association studies had detailed the criteria of the disease. The 2010 revised guideline focused on the magnetic resonance imaging (MRI) parameters and echocardiographic findings of the disease and familial link with genetic variations.[4]

Imaging of the right ventricular morpho-functional abnormalities with echocardiographic and magnetic resonance studies are important diagnostic tools and also endomyocardial biopsy has the potential for an in vivo demonstration of typical fibro-fatty replacement of RV muscle.

The management of the disease usually depends on the symptoms of the disease; pharmacological and non-pharmacological therapy is important in the management of the disease. Heart transplantation is generally the final therapeutic option with severe biventricular failure.

We describe the clinical progress of the three patients with ARVD/C and their final therapeutic management with orthotopic heart transplantation.

CASE REPORTS

CASE 1

21 year old male was admitted to another hospital with dyspnea and coughing symptom. He had hypothyroidism and family history of familial erthyrocytosis. He had phlebotomy because his hematocrit (Htc) level has increased 57.7%. His cardiac status evaluated, he had right bundle branch block, epsilon wave (reproducible low-amplitude signals between end of QRS complex to the onset of T wave) in the right precordial leads V_1 to V_3, QRS duration was >110 ms at his electrocardiogram (ECG) studies (Figure 1). His transthoracic echocardiography (TTE) had showed left ventricular ejection fraction (LVEF) 40%, tricuspid regurgitation was 3 to 4, pulmonary artery pressure was 30-35 mmHg, and his right atrium, right ventricle were dilated and right atrial systolic dimension was 6.8 cm and right ventricular systolic dimension was 5.5 cm in diameter.

Late June 2009, his cardiac MRI study shows diffuse focal dyskinetic areas, in right ventricular out-flow tract, there was aneurysmatic dilatation and epicardial-myocardial fatty infiltration which is diagnostic for ARVD/C.

He admitted our hospital late January 2011, on his admission his cardiac catheterization was reported as pulmonary capillary wedge pressure (PCWP) 13 mmHg, his systolic pulmonary artery pressure was 23 mmHg, diastolic pressure was 13 mmHg and the mean pressure was 9 mmHg. Cardiac out-put (CO) was 3.09 L/min, cardiac index (CI) was 1,8 L/min/m^2 and pulmonary vascular resistance was 2,3 woods/unit. He was New York Heart Association (NYHA) Class III. He had episodes of ventricular tachycardia attacks which he had intracardiac defibrillator (ICD) implantation.

September 2011, his hematocrit level was 53.2%, his hemoglobin level was 18.5 g/dL. He had phlebotomy 2 times, he was receiving anti-coagulant therapy with Coumadin, and his INR therapeutic level was between 2.5-3. His follow-up transthoracic echocardiography was done, his LVEF was 35%, there was thrombus formation in his right atrium 2.8x2.78 cm in diameter, 1.39x1.53 cm at right ven-

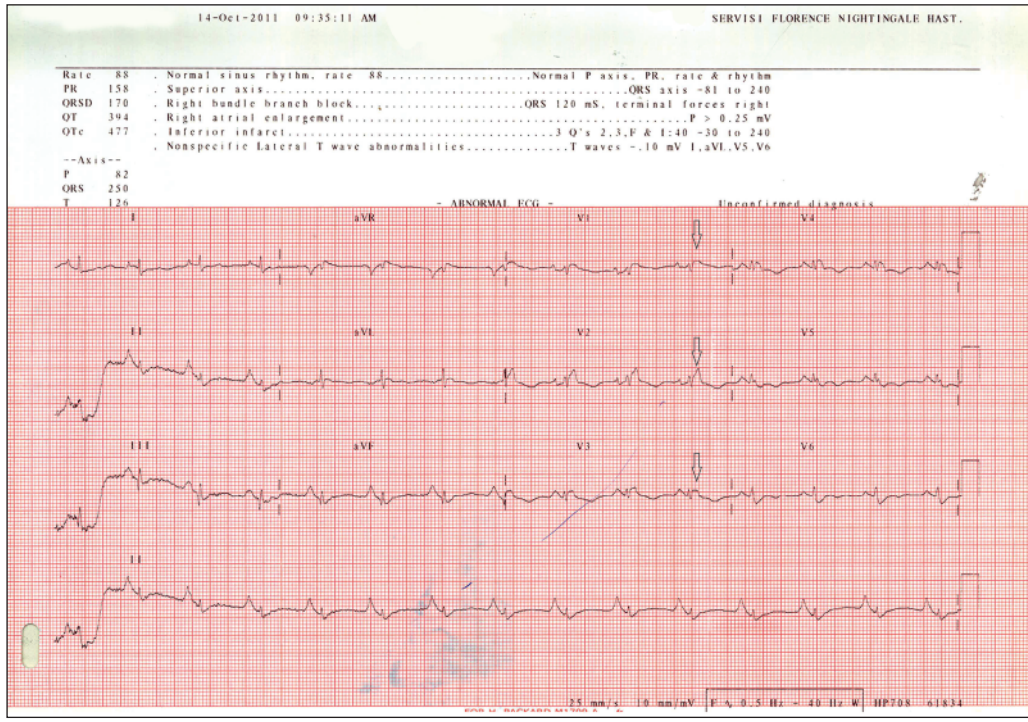

FIGURE 1: ECG from proband with epsilon wave V1-V3, atrial fibrillation, and right bundle branch block.

tricle attached to septal annulus and 1.7x2.04 cm in diameter at lateral wall (Figure 2). He was hospitalized, the anticoagulant therapy was switched to heparin infusion, we yielded a target a partial thromboplastin time (PTT) range of 80-100sec.

Mid-November 2011, he had orthotopic heart transplantation. The explanted native heart had the thrombus formation at his right atrium which was attached to right atrial wall (Figure 3). He was extubated next day and discharged from intensive care unit in post-operative 3 days. His native heart biopsy was reported as focal degeneration of myocytes, interstitial fibrosis and ischemic degeneration of papillary muscles, fatty infiltration (Figure 4). Morphologically the right ventricular wall was severely thinned and dilated, the thickness ratio of right ventricular wall to left ventricle wall is 0.4/1.5 cm (Figure 5).

He was status post heart transplant 36 months, his follow-up echo studies and endomyocardial biopsies (EMB) showed no sign of rejection. His last EMB was reported as Grade I. He had returned back to his work and get married, started to have active life.

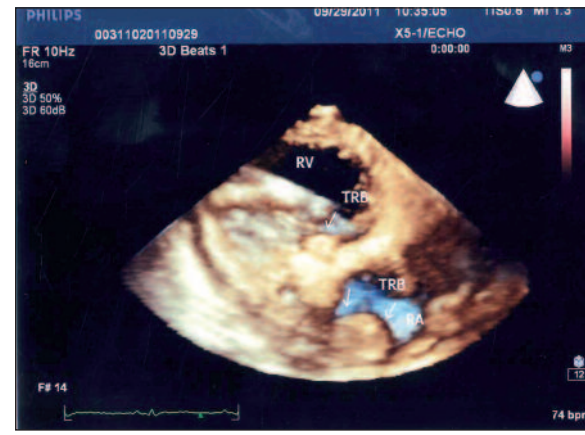

FIGURE 2: Intracardiac thrombus formation at right atrium and ventricle at echocardiographic study.

CASE 2

34 year old young woman was admitted another hospital with a history of syncope, palpitation vitiligo, psoriasis dermatiformis, Hashimato thyroiditis and asthma. She had systolic murmur 2/6 at tricuspid mezocardiac area, hepatomegaly during her admission at 2003. November 2006, she had holter monitoring was reported as 348 ventricular extrasystole and persistant atrial fibrillation, right

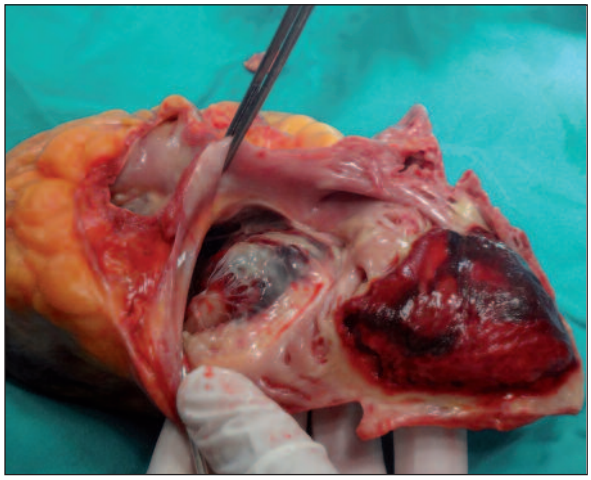

FIGURE 3: Right atrial thrombus formation at explanted ARVD/C heart specimen.

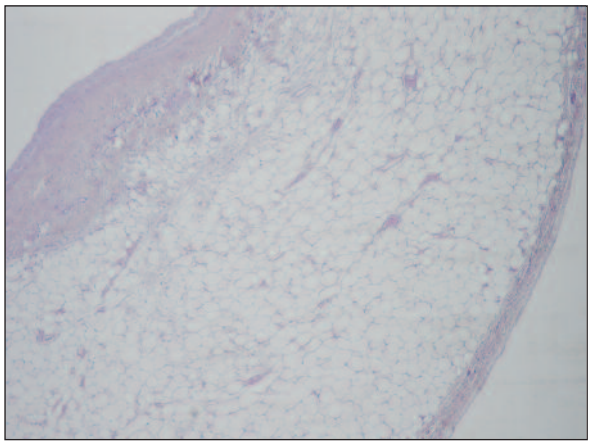

FIGURE 4: The whole cut section of the right ventricule shows three layers of heart; endocardium, myocardium, and pericardium. Extreme myocardial atrophy characterized by abundant adipose tissue and loss of myoctes could be seen (HE, x40).

bundle branch block (RBBB), epsilon waves and had ICD implantation. Her cardiac MRI was reported as ARVD/C with myocardial-epicardial fatty infiltration of the right ventricle.

Late November 2010, she was hospitalized at the same hospital as warfarin intoxication with an INR level of 12,5.

She admitted to our hospital at June 2011. She had her right ventricle ICD lead implantation and her cardiac catheterization was documented as; PCWP was 17 mmHg, PA was 28/14-19 mmHg, CO was 4,4 L/min, CI was 2,8 L/min/m^2 and right ventricular stroke work index (RVSWI) was 0.92 gm/m^2. Her echocardiographic studies showed that her right atrium was dilated 8.1x9.6cm in diameter and right ventricular fractional area contraction (RVFAC) was 30% and her LVEF was 40%. She was receiving heart failure medical treatment with high dose diuretic therapy to relieve her liver congestion secondary to her right her failure.

She had attempted a suicide by taking sleep medication due to sudden loss of her father and mother at October 2011. She had adult psychiatry consultation twice a week, was on rehabilitation therapy to prevent her mental and emotional disorders.

After weekly psychotherapy, sessions, she was decided to relist in the waiting list again due to her emotional progress of rehabilitation therapy.

Mid-December 2011, she had an heart offer and orthotopic heart transplantation. Her native heart specimen were inspected during explantation and the right atrium wall was so thin and transillumination can be observed (Figure 6). Post-operative 2nd day she was extubated and bi-level positive airway pressure (BIPAP) therapy was per-

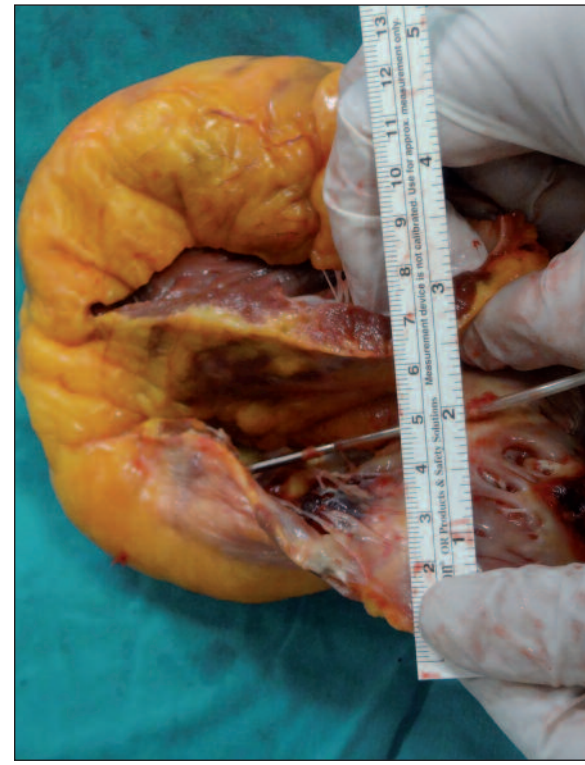

FIGURE 5: The wall thickness ratio of RV wall to LV wall at ARVD/C heart specimen.

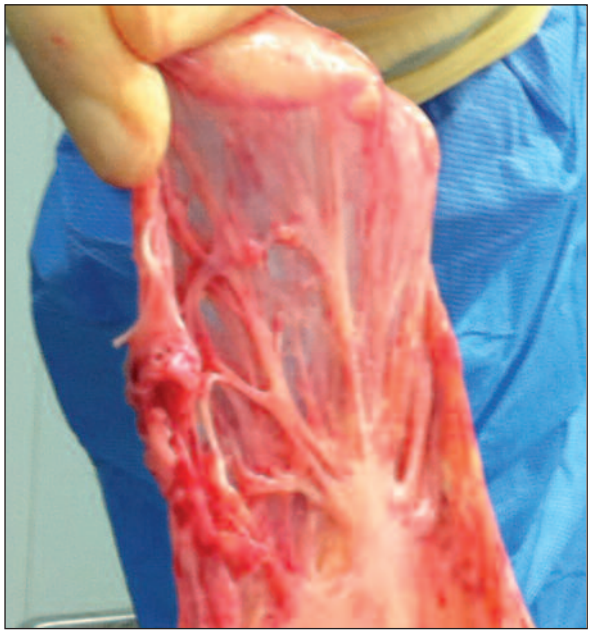

FIGURE 6: Morphological apperance of thin walled right atrium of an explanted ARVD/C heart specimen.

formed due to her blood gases worsening and respiratory acidosis. She was re-intubated and her bronchoalveolar lavage and her thoracal computed tomography was done. The secretions which were aspirated were white mucoid, thick and sticky secretions. She had antibiotic regimen for possible *Pneumocystis carinii* infection. She had elective tracheotomy so that she could rehab and take her fluids oral. Her *P. carinii* polymerase chain reaction (PCR) was negative. Her trachea cannula was removed postoperative 14 days and was discharged to home.

During her follow-up echocardiographic studies and endomyocardial biopsy results showed no sign of rejection. She was status post heart transplant 34th months and survives with a good quality of life as a graphic designer.

CASE 3

38 year-old man had a history of syncope and admitted to another hospital as of February 2002 and diagnosed as ARVD/C with his MRI findings. During his out-patient follow-ups, he had been on anticoagulant regimen since 2003, he had sustained ventricular tachycardia attacks and had ICD implantation at 2006.

He had a cerebrovascular event which was characterized by an infarct at his right temporo-fronto-parietal area at March 2009.

He admitted to our hospital with symptoms of right heart failure, peripheral edema, icteric, cyanosis, dyspnea and was NYHA Class III-IV at June 2012. He had a left sided sensory-motor hemiparesis due to right temporo-fronto-parietal infarct. His cardiac catheterization was reported as his PCWP was 21 mmHg, CO was 3,5 L/min, CI was 2.03 L/min/m^2 and RVSWI was 0,5 mg/m^2. His echocardiographic studies were; his LVEF was 40%, RV systolic diameter was 5cm, RV thickness was 0,7 cm, in apical area 0.5cm, right atrium systolic diameter was 7cm, right ventricular area contraction (RVFAC) was 35%, and had thrombus formation 6.3x3.3 cm in diameter at right atrial wall. RV wall motions at apical and lateral side was hypo-kinetic. He had received anti-coagulant regimen due to his echo findings. He was discussed at the medical board meeting with his echocardiographic and neurologic status. The patient and his family had ben informed about his high risk status.

He was listed as status 1A at mid-June 2012. His INR level was between 3,5 to 4,0. He had a heart offer at November 2012. He had orthotopic heart transplantation and hemodynamically stable and extubated post-operative next day. He was discharged from intensive care unite (ICU) to ward post-op 3rd day. Post-op 9th day, he had recurrent secondary generalized tonic-clonic seizures followed by left focal motor seizures at the same night under anticonvulsant medication. He was intubated electively, his cranial computed tomography and electroencephalography (EEG) were revealed that prior infarct area was the origin of the epileptic attacks.

He was not able to wean from the ventilator due to methicillin resistant *Staphylococcus epidermidis* infection and had tracheostomy. His antibiotic and anti-epileptic regimen organized, had chest physiotherapy and de-cannulated 1 week after his tracheostomy. He was discharged 20 days after his heart transplantation.

His follow-up echocardiographic studies reported as his right and left ventricular systolic and diastolic function were in normal ranges. He also

had his routine neurology out-patient follow-ups for his anti-epileptic regimen. His last endomyocardial biopsy was reported as Grade I. He is status post heart transplant in 24th months and doing well.

DISCUSSION

All three patients described in this report had typical echocardiographic features of ARVD/C and presented with most severe manifestations of the disease. All of them had intracardiac defibrillator (ICD) implantation due to ventricular tachycardia attacks which was documanted by their holter studies. Two patients were status 1A, were receiving heparin infusion due to their intracardiac thromboses, the other patient was status 1B.

All 3 patients had their disease managed by pharmacological therapy and their final therapeutic option was orthotopic heart transplantation due to biventricular failure and intracardiac thrombus formation due to low ejection fraction (EF), hypokinetic right ventricular wall motion, and dilated right atrial and ventricular chambers. According to Task Force Guidelines; two major criteria, one major and two minor criteria or four minor criteria are needed to diagnose the ARVD/C.[3] Due to 2010 guidelines newer the imaging studies like MRI and detailed two and three-dimension echo studies diagnosis criteria had been revised.[4] The disease usually is discovered early adulthood by the presence of ventricular arrhythmias. Our patients age were between 17 to 35 years when they have been diagnosed as ARVD/C.

They had malignant ventricular tachyarrhythmias and ICD implantation to terminate their arrhythmias. Long-term treatment with amiodarone is associated with high incidence of adverse effects and ICD implantation is needed for long-term treatment in young population.[4,5] The correct diagnosis of ARVD/C is important, the main differential diagnosis of idiopathic right ventricular tachycardia has curative treatment by catheter ablation.

The endomyocardial biopsy sensitivity is high, if samples were taken from the RV inferior-subtricuspid, antero-apical, and mid-outflow tract (RVOT), the septum, and the LV. Biopsy should be performed by experienced clinicians in selective centers so that perforation of the thin wall right ventricle would be prevented.[5] MRI also helps the diagnosis of ARVD/C and documents the overinterpretation of wall motion abnormalities and intramyocardial fat is commonly seen.

The risk stratification and the therapeutic strategy in ARVD/C depends on the electrophysiologic study (EPS), MRI, EMB and also genetic counseling determining the mutations in the desmosomal proteins.[6-11]

Our first patient had his genetic screening for mutations of desmosomal proteins, also his father had the same diagnosis, and the third patient had a family history of ARVD/C, and his elder brother managed by medical therapy.

ARVD/C has four phases which effects the risk stratification of the disease. The first phase is where individuals are asymptomatic but nonetheless are at risk of sudden death. The second phase symptomatic arrhythmias of RV origin are common and more prominent; the third phase the isolated RV failure and concomitant dysplastic process becomes diffuse with greater dilatation and dysfunction of RV and finally the fourth phase is left ventricular involvement and biventricular failure.[7-11]

All three patients had admitted our hospital with either third phase and fourth phase. The presence of biventricular heart failure and intracardiac thrombus formation were identified as high risk group for our patients. The presence of end stage heart failure and left ventricular involvement were risk factors for an adverse outcome to continue with pharmacological therapy. The two patients were at status 1A and hospitalized, received continuous heparin infusion therapy, weekly echocardiographic follow-up for their thrombus formation was done.

Dalal et al. had reported the Kaplan-Meier survival analysis of 100 ARVD/C patients. The median age at first presentation was 30 years. By the age of 60 years nearly 50% of their patients experienced cardiac death and half of the patients developed VT by the age of 41 year. Three of our patients were young, their mean average age was 30 years.[10]

Buja et al. had 14 of 312 ARVD/C patients (4,3%) died during the follow-up of these patients. The reasons of the fatal events were sud-

den death due to reported VT/VF 'electrical storm', intractable heart failure, infective endocarditis.[7]

There are no well-controlled studies comparing the efficacy of various anti-arrhythmic drugs.[11] High-risk group patients should be monitored closely if episodes of symptomatic VT are frequent and also LV involvement with depressed EF. There is a potential complication for high risk group of patients during ICD lead implantation in a diseased thin walled right ventricular myocardium, careful placement and assessment of the sensing and pacing threshold to prevent adverse events.

ARVD/C had been reported characterized by intrafamilial phenotype diversity, mostly an arrhythmic presentation in probands, more than 50% died suddenly.[7] These ARVD/C patients should be monitored closely by their physicians, to figure out how the disease progress in each phase, so appropriate timing of the listing of the patient for donor heart transplant waiting list is life-saving, before the secondary end-organ irreversible dysfunction occurs or sudden death.

Recently, right ventricular exclusion surgery (Fontan-type repair) has been used in patients with ARVD/C. Theoretically, ideal canditates for this surgery are the ones who had been suffering from only right ventricular failure. Patients with biventricular failure become better candidates for heart transplantation. No data are available concerning potential clinical benefit of cardiac resynchronization therapy in ARVD/C. If there is no contraindication for the patient to be listed for heart transplantation waiting list including the body mass index, malignancy and older age over 65 years. Heart transplantation is the best treatment modality with long-term survival.[12,13]

In our case series, orthotopic heart transplantation would be the final therapeutic option for our patients. All three patients had biventricular failure and had orthotopic heart transplantation and continued to survive with good quality of life.

We believe that the management therapy for ARVD/C to prescribe antiarrhtymic drugs like β-blockers and amiodarone, to perform catheter ablation or to implant an ICD and the final therapeutic option heart transplantation must be individualized based on risk assessment, clinicians decision and patients management with the disease.

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