International Journal of Healthcare Sciences ISSN 2348-5728 (Online)
Vol. 4, Issue 2, pp: (1410-1416), Month: October 2016 - March 2017, Available at: www.researchpublish.com

Pathogenesis and Roles of Treatment Arrhythmogenic Right Ventricular Cardiomyopathy: Review

[1]Sahli, Abdulaziz Ali Y, [2]Turki Hessen Anab, [3]Ismail Mohammed Taher Sumaily, [4]Yahya Ali Aljefri, [5]Zyad Ali Daghriri

Abstract: **Antiarrhythmic therapy is commonly used for suppression of arrhythmias in patients with arrhythmogenic best ventricular cardiomyopathy (ARVC) in conjunction with implantable cardioverter defibrillators (ICD) and catheter ablation. The efficacy of mix flecainide and sotalol/ metoprolol treatment for patients refractory to single representatives and/or catheter ablation has actually not been well established. The main aim of this review is to explain our experience in utilizing the addition of flecainide in combination with sotalol/ metoprolol for the treatment of arrhythmias in patients with ARVC. In conclusion, The addition of flecainide in mix with sotalol/ metoprolol may be an efficient antiarrhythmic strategy for the control of ventricular arrhythmias in patients with ARVC refractory to single agent therapy and/or catheter ablation.**

Keywords: **Antiarrhythmic therapy, sotalol/ metoprolol treatment, ventricular.**

1. INTRODUCTION

Arrhythmogenic ideal ventricular cardiomyopathy (ARVC) is an inheritable heart muscle disease identified by fibrofatty replacement of the ideal ventricular (Recreational Vehicle) myocardium[(1-6)]. Clinical symptoms relate to electrical instability, including either ventricular tachycardia (VT) of Recreational Vehicle origin or ventricular fibrillation (VF), which might lead to sudden death, mainly in young people or athletes. Ventricular arrhythmias become worse throughout or right away after exercise and participation in competitive sports has actually been connected with an increased risk for sudden death[(7-8)] . Later in the disease history, the RV becomes more diffusely included and left ventricular (LV) participation might lead to biventricular cardiac arrest[(5-6)].

The estimated prevalence of ARVC in the basic population ranges from 1 in 2000 to 1 in 5000. A familial background has been demonstrated in about 50% of ARVC cases. The disease affects males more often than ladies (with a ratio approximately 3:1) and becomes clinically obvious frequently in the 4th or third decade of life[(4,9-11)].

Clinical diagnosis of ARVC is often challenging because of the nonspecific nature of the disease and the broad spectrum of phenotypic manifestation, varying from serious to concealed types. In 1994[(12)] and 2010[(13)] The International Task Force proposed criteria for the clinical diagnosis of ARVC.

ARVC shows an autosomal dominant pattern of inheritance with incomplete penetrance and variable clinical expression[(14)], although an autosomal recessive variant has been identified[(15,16)]. Since the very first ARVC-causing gene (ie, plakoglobin gene-JUP) was determined in patients with Naxos disease, several anomalies of genes encoding desmosomal cell adhesion proteins have been detected in patients with ARVC[(9-11).] Molecular hereditary analysis is an effective tool for preclinical diagnosis of ARVC in asymptomatic member of the family of gene-positive probands and may add to run the risk of stratification and clinical management.

ARVC is likewise characterized by dysfunction of the cardiomyocyte junction inclining patients to ventricular arrhythmias, cardiac arrest, and sudden death [(17)] . Treatment is concentrated on slowing disease progression, minimizing the danger of sudden death, and palliating symptoms related to reoccurring arrhythmias and heart failure. The essentials of

therapy are positioning of implantable cardioverter-defibrillators (ICD) in symptomatic and high threat patients as well as treatment of arrhythmias through catheter ablation and antiarrhythmic medication [18]. While these therapies have actually substantially improved patient results, the danger of recurrent arrhythmias remains high [19]. In patients failing to attain arrhythmia control with single antiarrhythmic agents and/or catheter ablation, combination antiarrhythmic treatment may result in enhanced arrhythmia control. Nevertheless, little information exists to assist the option of combination antiarrhythmic representatives in this setting. In a current report, we characterized our preliminary experience with various antiarrhythmic combinations within our own friend of patients with RV cardiomyopathy [20]. Ever since we have expanded our cohort and in this report describe our follow up experience with using combination therapy in patients refractory to single representative therapy and/or catheter ablation, particularly highlighting the effectiveness of the combination of sotalol/ metoprolol and flecainide in patients with ARVC.

2. METHODOLOGY

Four databases were selected to ensure a comprehensive review of the literature: PubMed, EMBASE, Ovid, and the Cochrane Review up to 2015. On January 25, 2014, a total of 13 different queries were used for each engine: (1) “Arrhythmogenic right ventricular cardiomyopathy,” (2) “Antiarrhythmic therapy,” (3) “Ventricular Arrhythmia ,” (4) “Clinical electrophysiology,” (5) “Combination therapy ,” (6) “Genetics ,” (7) “Catheter ablation,” (8) “Implantable cardioverter defibrillator ,” (9) “Sudden cardiac death,” . A hand search of the tables of contents of relevant journals published from January to December 2015 was then performed .Patient cases and medication dosages are summarized in

Table 1.

3. RESULTS AND DISCUSSION

Case I: A 33 year old female was detected with ARVC on the basis of a heart MRI, ECHO and signal-averaged ECG. She went through placement of an ICD and attempted endocardial ablation of several VTs of right ventricular origin. She was treated with a variety of single antiarrhythmic agents consisting of metoprolol, amiodarone, sotalol, and propafenone but continued to have episodes of workout caused VT. Offered the frequent arrhythmias, flecainide was started and titrated to a dosage of 150mg BID in addition to her dose of sotalol 80mg BID. On this combination treatment her arrhythmia control has actually been excellent. She has been devoid of significant arrhythmias for over 116 months.

Case II: A 37 year old woman who was detected with ARVC on the basis of her ECG, ECHO, heart MRI, and electrophysiology research study after providing with an episode of exertional syncope. She was initially treated with an ICD and sotalol monotherapy but developed frequent VT in the setting of pregnancy. She was subsequently treated with the addition of flecainide leading to successful resolution of arrhythmias. Flecainide was terminated shortly after the birth of her kid, however because that time, the patient established recurrent ventricular arrhythmias triggering the re-introduction of flecainide to her medical routine. Ever since, she has been arrhythmia complimentary for 38 months with the mix of sotalol 240mg BID and flecainide 75mg BID.

Case III: A 66 years of age man identified with ARVC on the basis of particular abnormalities of the ECG, heart MRI and ventricular angiography. He was at first treated with ICD placement and amiodarone. His course was made complex, however, by the advancement of recurrent exercise induced VT triggering endocardial ablation and the advancement of extreme amiodarone induced dermatitis and lung infiltrates. Due to these side effects, his medical regimen was transitioned to the mix of sotalol 220mg BID and flecainide 50mg BID. The patient has been arrhythmia free for 46 months considering that beginning this mix.

Case IV: A 47 years of age guy was referred to our arrhythmia center after sustaining a cardiac arrest throughout workout and went through placement of an ICD. Further examination, however, revealed a positive family history of sudden death in his dad at age 37 and an ECHO with serious international right ventricular enlargement and apical aneurysm. Interrogation of his ICD revealed extra episodes of monomorphic VT. On electrophysiology research study he was kept in mind to have an arrhythmogenic area in the best ventricular outflow system which was ablated via an endocardial method. He was started on sotalol 80mg BID. The patient experienced excellent arrhythmia control for over 4 years in spite of an active lifestyle till January 2015 when he had the sudden beginning of persistent VT resulting in 8 ICD discharges. His sotalol dosage was increased to 240mg BID however this dosage was not bearable because of extreme tiredness and malaise. He was therefore started on flecainide 100mg BID and sotalol 160mg BID. Considering that initiation of mix treatment, he has actually stayed arrhythmia free for the last 22 months.

Case V: A 62 year old man was referred to our center for ventricular arrhythmias. He had his first episode of continual VT at the age of 31. At that time, he underwent endocardial ablation and was begun on amiodarone. At the age of 49 he had reoccurring VT and underwent placement of an ICD. He continued to experience frequent VT which prompted the transition of amiodarone to sotalol but cannot accomplish appropriate control with this program. Additional examination was substantial for an ECHO demonstrating a badly enlarged best ventricle and a standard ECG with T-wave inversions in leads V1-V6 permitting the diagnosis of ARVC to be made. At his initial go to in our arrhythmia clinic in April 2015, he was transitioned from sotalol to a combination of metoprolol succinate 50mg QD and flecainide 50mg BID. Because that time he has actually been arrhythmia complimentary for over 18 months.

Case VI: A 42 years of age guy was referred to our center for management of frequent ventricular arrhythmias. The patient was detected with ARVC at the age of 36 after sustaining recurrent episodes of monomorphic VT, abnormal heart MRI, T-wave inversions in leads V1-V4 on baseline ECG, and genes favorable for a pathogenic anomaly in TMEM43. He underwent ICD implantation, was begun on amiodarone, and underwent a series of epicardial and endocardial VT ablations for persistent VT at experienced outside medical facilities. Following the ablations, his amiodarone was transitioned to sotalol monotherapy. In spite of dosage adjustments of these medications and repeat ablation procedures, he continued to have frequent episodes of VT. He was referred to our center in January 2015 where he was begun on flecainide 50mg BID in addition to sotalol 120mg BID. 2 months after initiation of mix treatment, he had a recurrent episode of VT at a rate of 130bpm, much slower than his previous episodes and below the detection threshold of his ICD. He consequently went through modification of his ICD VT detection limit and an increase of the flecainide dosage to 100mg BID. After this dosage increase, he had one more episode of steady VT at a rate of 117bpm, once again under the detection limit of the ICD (Figure 2). He just recently underwent a repeat endocardial ablation and was classified as a failure of combination treatment although the VT rate reduced considerably after treatment. He is now devoid of VT on sotalol alone.

Case VII: A 37 years of age male was described our center after an episode of palpitations and pre-syncope while running. Develop revealed a bigger right ventricle on ECHO and T-wave inversions in leads V1-V3 on ECG consistent with ARVC. On electrophysiology research study he was found to have inducible VT and proof of an epicardial scar prompting positioning of an ICD. He was furthermore begun on metoprolol. Regardless of beta-blocker therapy, the patient received a number of ICD discharges triggering him to go through epicardial/ endocardial ablation at another medical center. The ablation was regrettably complicated by pericardial effusion and tamponade needing pericardiocentesis. Consequently, the patient experienced recurrent ICD discharges and an epicardial/ endocardial ablation was duplicated. This treatment was made complex by tear of the LV wall necessitating emergent surgical repair. His post-operative course was complicated by development of an epicardial abscess which was surgically drained pipes, mild reduction in his left ventricular ejection fraction to 45%, and persistence of symptomatic PVCs and NSVT. He was briefly trialed on sotalol but could not endure the medication due to fatigue. He was then started on mexiletine 200mg TID which lowered the concern of his PVCs. Within one year, nevertheless, the patient developed frequent episodes of VT and underwent numerous ICD discharges. Offered the reoccurring VT, he was transitioned from mexiletine to flecainide 150mg BID in addition to metoprolol 25mg BID. Considering that the initiation of flecainide the has actually been free of VT for the last 24 months.

Case VIII: A 52 year old guy was referred to our center for additional management of ventricular arrhythmias. The patient was detected with ARVC in his 20s after presenting with VT in the setting of a snake bite. He went through placement of an ICD and endocardial ablation. He was treated with amiodarone for a variety of years and consequently transitioned to bisoprolol. In 2015, he had an increase in his VT problem (which was mainly exercise induced) triggering initiation of sotalol 120 mg BID however did not accomplish appropriate arrhythmia control. He went through repeat endocardial ablation and flecainide 150mg BID was contributed to his routine. Despite initiation of mix treatment, within two months of follow up, the patient was kept in mind to have two episodes of VT ended with ATP upon interrogation of his ICD representing failure of combination therapy. In addition, he established adverse effects of fatigue and dysguesia connected with the brand-new mix. He consequently went through combined endocardial and epicardial ablation and has been taken off sotalol. He is presently being evaluated for a repeat ablation after cannot attain control on a regimen of flecainide 100mg BID and metoprolol 25mg BID.

4. DISCUSSION

Our experience highlights the reliable use of combination sotalol/ metoprolol and flecainide in patients with ARVC suffering from recurrent arrhythmias in spite of multiple previous medication trials. In addition, although combined endocardial/epicardial catheter ablation has actually recently been demonstrated to have sensible efficacy in ARVC patients with medium term follow-up [21,22], in patients with reoccurring VT after several epicardial ablations, or complications such as heart tamponade, the alternatives for extra catheter based intervention are restricted. The use of mix antiarrhythmic treatment in such patients may supply a remarkable improvement in quality of life. These findings are important as there has actually been a paucity of data guiding using combination therapy in ARVC.Several past studies have actually evaluated the use of mix antiarrhythmic agents in ARVC nevertheless prior experience with the addition of flecainide in mix therapy is very limited. One of the first trials to suggest effectiveness of combination therapy in ARVC was released by Tonet et al. in 1988 [23]. In this research study, 31 patients with refractory VT were successfully handled with the combination of amiodarone and beta-blocker. Just 4 of the patients in this research study were understood to have ARVC. Quickly following, Lequeret et al. released a report documenting their experience treating 58 ARVC patients with a number of antiarrhythmic mixes [24] .The particular combinations included class I agents + beta blocker, class I agents + amiodarone, and amiodarone + beta blocker. Efficacy was developed by evaluating arrhythmia reoccurrence within 1 year of follow up. The mix of class I representatives + beta blockers proved to be effective in 35% of patients, amiodarone + Class I representatives worked in 58% of patients, and the combination of amiodarone + beta blocker was effective in 100% of patients although only 6 patients were treated with this combination.

The biggest trial examining the use of antiarrhythmic representatives in ARVC was released in 1992 by Wichter et al [25] .In this trial, the response to numerous antiarrhythmic agents was assessed throughout electrophysiology research study in order to assist outpatient treatment. In the initial study, 81 patients were followed for several months on various antiarrhythmic agents. Of these patients, 37 patients were treated with mix treatment after failure of response to single agents. The combinations examined were class I agent + beta blocker, class I representative + sotolol, class I representative + amiodarone, and 2 class I representatives simultaneously. Of these combinations, 2 concurrent class I representatives and Class I agent + beta blocker were inefficient in all patients examined. The combinations of class I agent + amiodarone and class I agent + sotalol however were effective in a small number of patients refractory to single representative therapy. The outcomes of the research study were later broadened to consist of 191 patients with comparable outcomes [26] .On the other hand, mix treatment including flecainide and sotalol/metoprolol worked in 6/8 patients in our research study. This may be due to the fact that flecainide was used instead of other class I drugs.

While incompletely understood, it is possible that the supporting impact of flecainide in our patients might be mediated through its effect on calcium homeostasis. This is supported by the reality that most of arrhythmias within our cohort were exercise caused. It has actually been revealed that, in addition to its action on sodium channels, flecainide impacts calcium homeostasis by antagonism of the ryanodine receptor [27,28] .This system has been postulated as the factor for its demonstrated effectiveness in the treatment of VT in patients with catecholaminergic polymorphic ventricular tachycardia [29] .The function of calcium homeostasis in ARVC is less well specified, nevertheless mutations in proteins with key roles in calcium homeostasis have been noted in patients with ARVC particularly phospholomanban [30], a regulator of the sarcoplasmic reticulum Ca++- ATPase, ankyrin-b [31], a binding protein crucial in the function of the Ca++/ Na+ exchanger, and the ryanodine receptor [32] Mutations in these specific genes were looked for but not recognized within our patient cohort.

It is also essential to keep in mind that the addition of flecainide in our patient sample has been well endured and not connected with any significant unfavorable occasions. Regardless of the historic doubt in using this medication in patients with structural cardiovascular disease provided the outcomes of the CAST trial, our outcomes suggest that this class of medication might play a significant role as an accessory in the treatment of patients with ARVC. It ought to be highlighted, nevertheless, that of our patients other than Case I and Case VII had a typical or near regular left ventricular ejection portion and all patients were secured by an ICD.

The reason for failure of single agent therapy in our patients is unclear. Offered the broad spectrum of disease phenotypes in patients with ARVC, it can be postulated that particular disease attributes may put patients at greater danger of reoccurring arrhythmias. Several groups have actually commented on specific imaging and ECG findings that might recognize greater risk functions of the disease and therefore anticipate the recurrence of arrhythmias in ARVC. In a retrospective analysis, Peters et al. reported that the presence of significant ideal ventricular dilation and left ventricular

dysfunction on ECHO as well as T- wave inversions beyond lead V3 on ECG were correlated with a higher threat of arrhythmia recurrence and bad antiarrhythmic response [33]. These observations were supported by research studies assessing threat aspects for unexpected cardiac death in patients with ARVC [34]. Within our own accomplice, all of the patients explained above have considerable right ventricular dilatation on imaging, 7/8 have T-wave inversions past V3, and one patient has actually documented left ventricular involvement. Therefore, it is most likely that the need for mix therapy to attain arrhythmia control highlights the presence of sophisticated or more aggressive disease. In our experience, the most common reason for initiation of combined treatment was drug failure (7/8) or drug intolerance (1/8) in addition to failure to respond to one or more encodardial or combined endocardial/epicardial ablations (7/8).

A number of essential restrictions of our study warrant reference. This report explains a single center experience with a small number of patients, thus the generalizability of our findings might be restricted. However, this reflects the truth of studying patients with an unusual disorder who have actually failed first- line therapy. Second, given that patient management was not standardized prior to initiation of combination therapy and was at the discretion of referring doctors, differential exposure to various antiarrhythmic medications, may have played a role in patient results. Finally, all patients within our friend were safeguarded with ICDs, thus our conclusions need to be just be applied to patients without ICD defense with extreme caution. Finally, while relatively efficient, the subsequent duration for a variety of our patients is relatively limited. Longer duration of follow up would be necessary to develop the toughness of our findings. Our experience suggests that mix therapy particularly with sotalol/ metoprolol and flecainide may be a crucial adjunctive therapy in ARVC patients with refractory arrhythmias. In spite of the constraints, it is important to stress that this mix treatment was discovered efficient for patients with ARVC and VT storm, VT happening in labor, and in patients refractory to numerous medication trials and ablation treatment.

Table 1: Patient characteristics

Patient	age	sex	Exercise/ Catechola-mine provoked VT	Ablation	Past medicati-on trials	Current medical regimen	Arrhyth-mia free period*	Genetics
I	45	F	YES	Endocardial	Metoprolol, Propafenone, Amiodarone	Flecainide 150mg BID + Sotalol 80mg BID	116 months	Declined testing
II	41	F	YES	None	Sotalol	Flecainide 150mg BID + Sotalol 240mg BID	38 month	PKP2 mutation
III	69	M	NO	Endocardial	Amiodarone, Sotalol	Flecainide 50mg BID + Sotalol 220mg BID	46 months	No mutations identifed
IV	54	M	YES	Endocardial	Metoprolol, Sotalol	Flecainide 100mg BID + Sotalol 160mg BID	22 months	DSG2 mutation
V	63	M	YES	Endocardial	Amiodarone, Sotalol	Flecainide 50mg BID + Metoprolol Succinate 25mg QD	18 months	DSP, PKP2, ALMS1 mutations (VUS)
VI	43	M	NO	Endocardial / Epicardial	Sotalol, Metoprolol	Flecainide 50mg BID + Sotalol 120mg BID	Failure of therapy	TMEM43 mutation
VII	41	M	YES	Endocardial / Epicardial	Sotalol, Metoprolol	Flecainide 150mg BID + Metoprolol 25mg BID	24 months	Declined testing

5. CONCLUSION

The addition of flecainide in mix with sotalol/ metoprolol proved to be efficient in controlling frequent arrhythmias in ARVC patients refractory to single agent antiarrhythmic treatment and catheter ablation over a considerable subsequent period.

REFERENCES

[1] Thiene G, Nava A, Corrado D, et al. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 1988;318:129e33.

[2] Basso C, Corrado D, Marcus FI, et al. Arrhythmogenic right ventricular cardiomyopathy. Lancet 2009; 373:1289e300.

[3] Basso C, Thiene G, Corrado D, et al. Arrhythmogenic right ventricular cardiomyopathy. dysplasia, dystrophy, or myocarditis? Circulation 1996;94: 983e91.

[4] Corrado D, Basso C, Thiene G, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multi- center study. J Am Coll Cardiol 1997;30:1512e20.

[5] Corrado D, Basso C, Thiene G. Arrhythmogenic right ventricular cardiomyopathy: diagnosis, prog- nosis, and treatment. Heart 2000;83:588e95.

[6] Corrado D, Basso C, Thiene G. Arrhythmogenic right ventricular cardiomyopathy: an update. Heart 2009; 95:766e73.

[7] Corrado D, Basso C, Schiavon M, et al. Screening for hypertrophic cardiomyopathy in young athletes. N Engl J Med 1998;339:364e9.

[8] Corrado D, Basso C, Pavei A, et al. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA 2006;296:1593e601.

[9] Sen-Chowdhry S, Syrris P, McKenna WJ. Genetics of right ventricular cardiomyopathy. J Cardiovasc Elec- trophysiol 2005;16:927e35.

[10] Corrado D, Thiene G. Arrhythmogenic right ventric- ular cardiomyopathy/dysplasia: clinical impact of molecular genetic studies. Circulation 2006;113: 1634e7.

[11] Sen-Chowdhry S, Syrris P, McKenna WJ. Role of genetic analysis in the management of patients with arrhythmogenic right ventricular dysplasia/ cardiomyopathy. J Am Coll Cardiol 2007;50: 1813e21.

[12] McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardio-myopathy. Task force of the working group myocar- dial and pericardial disease of the european society of cardiology and of the scientific council on cardiomyopathies of the international society and federation of cardiology. Br Heart J 1994;71: 215e8.

[13] Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/ dysplasia: proposed modification of the task force criteria. Eur Heart J 2010;31:806e14.

[14] Nava A, Bauce B, Basso C, et al. Clinical profile and long-term follow-up of 37 families with arrhythmo- genic right ventricular cardiomyopathy. J Am Coll Cardiol 2000;36:2226e33.

[15] McKoy G, Protonotarios N, Crosby A, et al. Identifi- cation of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). Lancet 2000; 355:2119e24.

[16] Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. Hum Mol Genet 2000;9:2761e6.

[17] Calkins H. Arrhythmogenic right ventricular dysplasia/cardiomyopathy – three decades of progress. Circ J. 2015; 79:901-13.

[18] Rigato I, Corrado D, Basso C, Zorzi A, Pilichou K, Bauce B, Thiene G. Pharmacotherapy and other therapeutic modalities for managing arrhythmogenic right ventricular cardiomyopathy. Cardiovasc Drugs Ther. 2015; 29:171-7.

[19] Dalal D, Jain R, Tandri H, et al. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. J Am Coll Cardiol 2007; 50:432–440.

[20] Ermakov S, Hoffmayer KS, Gerstenfeld EP, Scheinman MM. Combination drug therapy for patients with intractable ventricular tachycardia associated with right ventricular cardiomyopathy. Pacing Clin Electrophysiol. 2014; 37:90-4.

[21] Santangeli P, Zado ES, Supple GE, et al. Long-Term Outcome With Catheter Ablation of Ventricular Tachycardia in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy. Circ Arrhythm Electrophysiol. 2015; 8:1413-21.

[22] Philips B, Madhavan S, James C, et al. Outcomes of catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/cardiomyopathy. Circ Arrhythm Electrophysiol. 2012; 5:499-505.

[23] Tonet J, Frank R, Fontaine G, Grosgogeat Y. Efficacy of the combination of low doses of beta- blockers and amiodarone in the treatment of refractory ventricular tachycardia. Arch Mal Coeur Vaiss. 1989; 82:1511-7.

[24] Leclercq JF, Coumel P. Characteristics, prognosis and treatment of the ventricular arrhythmias of right ventricular dysplasia. European heart journal. 1989;10 Suppl D:61-7.

[25] Wichter T, Borggrefe M, Haverkamp W, Chen X, Breithardt G. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. Results in patients with inducible and noninducible ventricular tachycardia. Circulation. 1992;86:29-37.

[26] Wichter T, Paul TM, Eckardt L, Gerdes P, Kirchhof P, Böcker D, Breithardt G. Arrhythmogenic right ventricular cardiomyopathy. Antiarrhythmic drugs, catheter ablation, or ICD? Herz. 2005; 30:91-101.

[27] Hilliard FA, Steele DS, Laver D, Yang Z, Le Marchand SJ, Chopra N, Piston DW, Huke S, Knollmann BC. Flecainide inhibits arrhythmogenic Ca2 waves by open state block of ryanodine receptor Ca2release channels and reduction of Ca2 spark mass. J Mol Cell Cardiol 2010; 48:293– 301.

[28] Watanabe H, Chopra N, Laver D, Hwang HS, Davies SS, Roach DE, Duff HJ, Roden DM, Wilde AA, Knollmann BC. Flecainide prevents catecholaminergic polymorphic ventricular tachycardia in mice and humans. Nat Med. 2009;15:380-3.

[29] Van der Werf C, Kannankeril PJ, Sacher F, et al. Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia. J Am Coll Cardiol. 2011; 57:2244-54 .

[30] Van der Zwaag PA, van Rijsingen IA, Asimaki A, et al. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. Eur J Heart Fail. 2012; 14:1199-207 .

[31] Roberts JD, Wright PJ, Makara M, et al. Pathogenic Ankyrin-B Mutation and Exercise: A Novel Gene-Environment Interaction Predisposing to Arrhythmogenic Right Ventricular Cardiomyopathy. Heart Rhythm Conference. May 2015.

[32] Milting H, Lukas N, Klauke B, Körfer R, Perrot A, Osterziel KJ, Vogt J, Peters S, Thieleczek R, Varsányi M. Composite polymorphisms in the ryanodine receptor 2 gene associated with arrhythmogenic right ventricular cardiomyopathy. Cardiovasc Res. 2006 71:496-505 .

[33] Peters S, Peters H, Thierfelder L. Risk stratification of sudden cardiac death and malignant ventricular arrhythmias in right ventricular dysplasia-cardiomyopathy. International journal of cardiology. 1999;71:243-50.

[34] Wichter T, Corrado D, Paul M. Risk. Stratification and antiarrhythmic drug therapy. In: Marcus FI, Nava A, Thiene G (eds). Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. Milan, Italy: Springer Verlag, 2007 pp. 45–52.