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J wave syndrome: Benign or malignant?

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Review Article

Abstract

J wave syndrome is an electrical disease of the heart due to pathologic early repolarization. It encompasses a clinical spectrum from aborted sudden cardiac death due to ventricular arrhythmia (VA) usually in young affected patients to self-terminating ventricular ectopies, and finally, asymptomatic relatives of probands detected during electrocardiography acquisition (early repolarization pattern). This syndrome consists of 2 phenotypes, early repolarization and Brugada syndrome. Herein, we first describe 2 patients with early repolarization and Brugada syndrome, then, discuss their definition, epidemiology, genetics, cellular mechanism, diagnosis, risk stratification, and finally, therapeutic challenges and options one by one in detail.

Keywords: Brugada Syndrome; Sudden Cardiac Death; Ventricular Tachycardia

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Introduction

The J point is defined as the junction between the end of the QRS complex and beginning of the ST segment, where depolarization ends and repolarization begins on the action potential curve.[1,2] A prominent J point in an electrocardiogram (ECG), known as the Osborn wave, was described in hypothermia and hypercalcemia long ago.[2,3] It was first described in a frozen man by Tomaszewski in 1938[4] followed by the study by Osborn on hypothermic dogs in 1953.[5] Early repolarization pattern (ERP), a distinct J wave or J point elevation[3] in conjunction with downward concavity elevation of the ST segment, was described by Wasserburger and Alt in 1961.[6] It was considered as a benign ECG variation in the following decades.[7] However, in 1999, Gussak and Antzelevitch discussed the possibility of ventricular arrhythmia (VA) in some cases of ERPs,[8] which led to the concept of early repolarization syndrome (ERS). Moreover, in 1984, Otto et al. reported 3 cases of VA in young Southeast Asian men during sleep.[9] These patients had no structural heart disease and the only finding was a prominent J wave accompanied by ST segment elevation on their ECG.[1,2] Later, in 1992, Pedro, Ramon, and Josep Brugada described 8 patients with no structural heart disease and sudden cardiac death, with right bundle branch block morphology and ST segment elevation in V1 to V3 on ECG,[10] a condition known as Brugada syndrome (BrS). Growing evidence suggests that despite the differences of BrS and ERS in terms of the magnitude of J wave abnormality and location of ECG presentation, they are actually different points in a spectrum known as J wave syndrome. In this article, 2 cases are presented and the literature is discussed about different aspects of this newly introduced syndrome.

Materials and Methods

Case 1: A 36-year-old man was referred to our clinic due to recurrent episodes of paroxysmal palpitation and presyncope during the previous year. Past medical, drug, and family history were unremarkable. Serum electrolytes and transthoracic echocardiography (TTE) were normal. Figure 1 shows baseline ECG, including downward ST segment elevation in V1-2 and incomplete right bundle branch block. Due to high suspicion of VA, he was admitted for cardiac monitoring and further evaluation.

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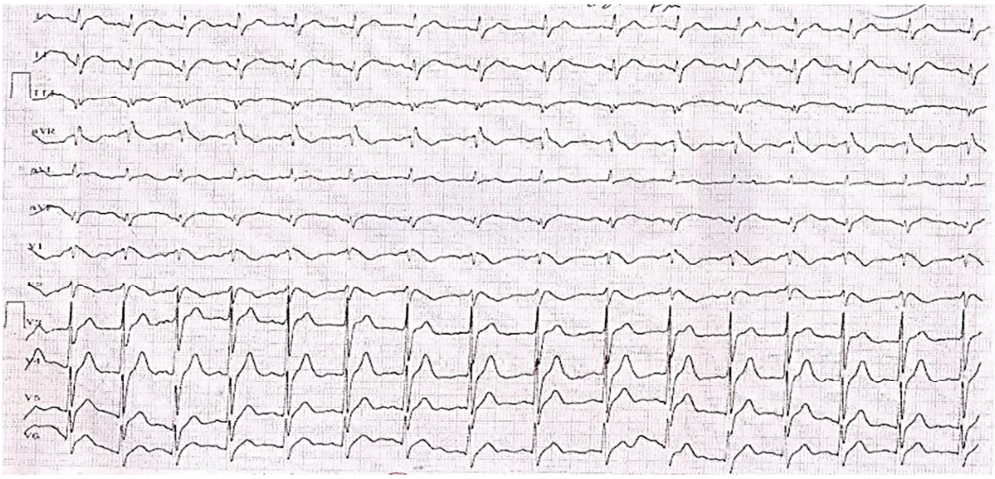

Figure 1. Baseline electrocardiogram (ECG) shows downward ST segment elevation in V1-2 and incomplete right bundle branch block

Figure 2 shows ventricular fibrillation (VF) documented by 3-channel ECG Holter monitoring. He received a dual chamber implantable cardioverter defibrillator (ICD), and within the last 6 years, he has not experienced any appropriate ICD shocks.

Case 2: A 32-year-old man presented to a local hospital due to aborted sudden cardiac death. Figure 3 shows the ECG strip in the emergency room. He received electrical cardioversion several times. In the emergency room, past medical, family, and drug history were negative. After initial stabilization, laboratory evaluation, echocardiography, and coronary angiography were performed, which were normal. Figure 4 shows baseline ECG with early repolarization pattern. Genetic study (exome sequencing panel) did not show any pathogenic variants. He has received single chamber ICD since 2017 and for the past 3 years, he has been on quinidine, and due to its shortage in our country, is now receiving cilostazol. Since the implantation, he has not received any ICD shocks.

Epidemiology

ERP is a common ECG finding with a prevalence of 5-30% in the general population.[11-13] It is more common in men (70% of the subjects),[2,11,12,14] and has an inverse relationship with age with a decline in its prevalence in middle-aged individuals.[2,11] Sinner et al. reported a prevalence of 13.1% in the German MONICA study,[13] and Tikkanen et al found a prevalence of 5.8% in a Finnish population;[15] both studies were conducted in middle-aged people. In a study conducted in Iran, the prevalence of early repolarization was 9.6% in healthy individuals of 20-60 years of age.[12]

Early repolarization is more common in athletes and physically active young men.[16] For instance, in a study, 14% of competitive athletes had J wave on ECG.[11] An ethnic relationship has also been reported. It is more prevalent in Southeast Asians and African Americans.[16] An association has also been reported between ERP and cocaine use,[8] lower systolic blood pressure,[12] left ventricular hypertrophy,[17] hypertrophic cardiomyopathy,[8] and left ventricular false tendon.[18]

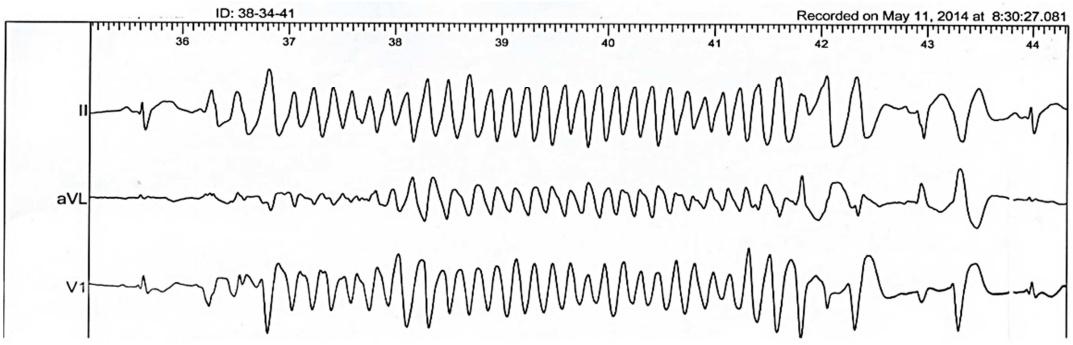

Figure 2. Electrocardiogram (ECG) shows initiation and termination of ventricular fibrillation (VF)

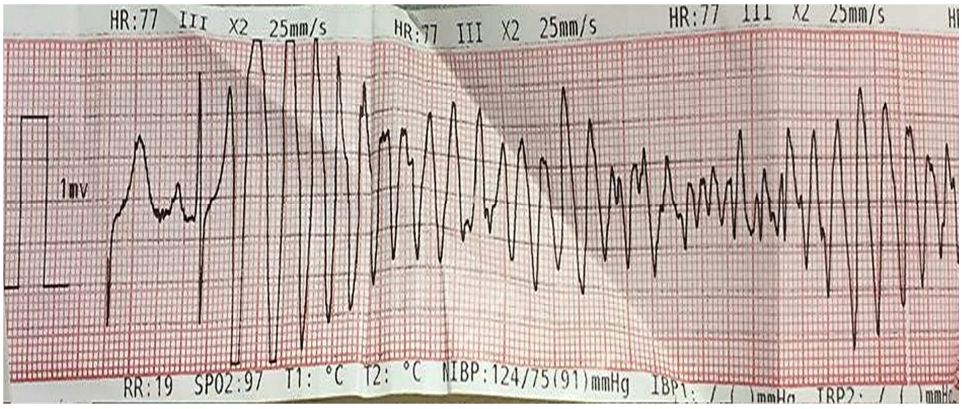

Figure 3. Electrocardiogram (ECG) shows initiation of ventricular fibrillation (VF) with early coupled premature ventricular complexes (PVC)

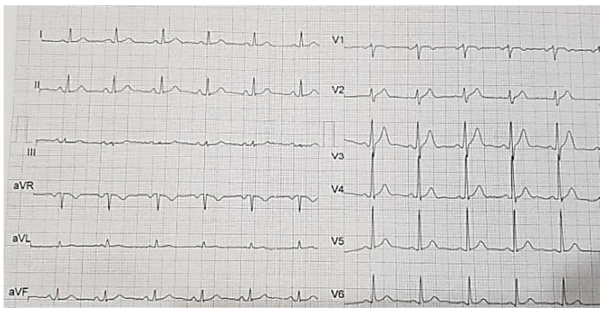

Figure 4. Baseline electrocardiogram (ECG) shows near normal parameters except for early repolarization pattern (ERP)

In a study conducted in young healthy men of 20-45 years of age in northeastern Thailand, early repolarization was found in 10.3% of the subjects, which had an association with the Sokolow-Lyon index for left ventricular hypertrophy (Odds ratio was 1.09).[19]

BrS is one of the most common causes of sudden cardiac death in men under 40 years old.[20] Its prevalence is about 5 in 10000 individuals. However, the Brugada pattern is more prevalent and 0.19% of healthy individuals had Brugada type ECG in one study, while most of them did not experience any episodes of VA or sudden death in a 10-year follow-up.[21] BrS usually presents in adulthood, and most patients become symptomatic between 20 and 65 years of age. Similar to ERS, it is more common in men and Southeast Asians.[22] In a large study, up to 94% of the patients with BrS who experienced cardiac arrest were male.[3]

Definition and classification

One of the older definitions of ERP is notching or slurring at the end of the QRS complex, an up-sloping ST segment elevation, and a tall symmetrical T wave.[7,8] This pattern is usually seen in the inferior or lateral ECG leads. It has also been reported that ST segment elevation is more prominent in mid to lateral precordial leads, and reciprocal ST depression in a VR can aid in the diagnosis of ERP.[8] More recent definitions focus on the J point elevation along with a terminal QRS notch, noting that ST segment elevation may be present or absent on a baseline ECG.[2,3] In one definition, ERP is considered as a J point elevation of 1 millimeter (mm) or more manifesting as slurring or notching at the end of the QRS complex in 2 contiguous leads.[14] According to the latest reports, ERP is defined as follows: 1) presence of a notch (entirely above baseline) or slurring (onset above baseline) in the downslope of the R wave; 2) peak of notch (J peak) equal to or more than 1 mm in at least 2 contiguous leads except for V1-V3; 3) QRS duration of less than 120 milliseconds in the leads with no notch or slurring.[3,7]

Antzelevitch and Yan[1] and Antzelevitch et al.[3] have described 3 types of ERP. Type 1 is predominantly in the lateral precordial leads, is more common in healthy young athletes, and is associated with a low risk of arrhythmia. Type 2 manifests in the inferior and inferolateral leads and is associated with a moderate risk of VA, but it can also be seen in young healthy men. Type 3 has the highest risk of arrhythmic, is occasionally associated with ventricular electrical storms, and involves lateral, inferior, and right precordial leads.[1,3] Tikkanen et al. have provided a different classification based on the characteristics of J point-ST elevation: 1) J point with ascending ST segment (benign form) and 2) J point with horizontal or descending ST segment (malignant form).[15]

Regarding BrS, 3 different ECG patterns have been defined, but not all of them among the diagnostic criteria of this syndrome. Type 1 is defined as a coved ST segment elevation equal to or

more than 2 mm in at least 1 right precordial lead (V1-V3) followed by T wave inversion. Type 2 is characterized by a saddleback ST segment elevation equal to or more than 2 mm and a biphasic or positive T wave. Type 3 is described as a coved or saddleback ST segment elevation of less than 1 mm.[3,20] Type 2 and type 3 are not diagnostic for BrS.

Genetic predisposition

ERS is related to genetic mutations, and more than 7 genes have been identified. They include similar genes with BrS: SCN5A, CACNA1C, CACNB2B, CACNA2D1, and KCNJ8 ($I_{K\text{-}ATP}$).[23,24] Mutation in the ankyrin-2 gene (ANK2) was also reported in two patients with ERP and VA.[25] ERS has a familial inheritance. In a study by Noseworthy et al., the prevalence of early repolarization was 11.6% in the family members of subjects with ERP with an odds ratio of 2.22.[17] However, due to the high prevalence of ERP in the general population, it seems that this condition is polygenic and is affected by nongenetic factors.

More than 12 different genes are associated with BrS. Loss of function mutations in SCN5A (Na channel) are reported in up to 28% of probands. About 13% of other probands have mutations in CACNA1C, CACNB2b, and CACNA2D1 (Ca channel).[26] Other less common mutations include SCN10A, SCN1B, SCN3B, KCNE3, KCNJ8, and KCND2. All these mutations result in the loss of function of I_{Na} and I_{Ca} (Na and Ca currents, respectively), and the gaining of function of I_{to} and $I_{K\text{-}ATP}$ (transient outward K current and ATP sensitive K current, respectively). It seems that over activation of I_{to} and $I_{K\text{-}ATP}$ currents plays an important role in the pathogenesis of J wave syndrome.[23,24] BrS has an inherited pattern that seems to be autosomal dominant with incomplete penetrance. Mutation in SCN5A, the most common mutation in BrS, is more common in familial versus sporadic patients.

The above evidence regarding the pattern of inheritance has led to debates on the genetic testing of the proband's family members. A major problem is that 3-5% of the general population have benign variants of SCN5A, leading to false positive results.[3] Currently, the 2017 AHA/ACC/HRS Guideline for Management of Patients with VAs and the Prevention of Sudden Cardiac Death has a class III (no benefit) recommendation for genetic testing in patients with ERP on ECG.[27] For BrS, the above guideline has a class I recommendation for genetic counseling and testing in the first-degree relatives of patients with BrS. Furthermore, in this guideline, there is a class IIb recommendation for genetic counselling and testing in patients suspected of or with definitive diagnosis of BrS. The latter recommendation is only for patients with spontaneous type 1 Brugada ECG. Moreover, the 2015 ESC Guidelines for the Management of Patients with VAs and the Prevention of Sudden Cardiac Death indicates difficulties in the recommendation regarding its polygenic nature, lack of evidence for familial transmission, and uncertainties in predicting this pattern as a predictor of sudden death.[28] The HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes indicates that there is no recommendation for family screening in patients with asymptomatic ERP.[29]

Cellular mechanisms

The I_{to} current plays an important role in the presence of J wave on ECG. The distribution of I_{to} is not uniform in the myocardial thickness, thus resulting in a prominent action potential (phase 1) notch in the epicardium, but not in the endocardium.[1] This situation leads to a transmural voltage gradient. The terminal notch of the QRS complex (J wave) is considered to be a result of intraventricular conduction delay. Factors influencing the I_{to} current can affect the J wave. For instance, I_{to} is reduced following tachycardia due to slow recovery. Thus, J wave is diminished in tachycardia (after administration of isoproterenol) and is accentuated in bradycardia (after administration of verapamil or propranolol).[26] Furthermore, drugs with I_{to} blocking properties, like quinidine, can decrease the J wave amplitude and diminish the ST segment elevation. It should be noted that a decrease in inward I_{Ca} or I_{Na} currents or an increase in the outward $I_{K\text{-}ATP}$ current can also accentuate the J wave on ECG.[8,26] I_{KAS} (calcium activated potassium current) is also associated with ERP.[30,31] The right ventricular epicardium has a prominent I_{to} current, resulting in an accentuated transmural voltage gradient; moreover, the presence of ST segment elevation in the right precordial leads in BrS.

The repolarization hypothesis in BrS suggests that intensified outward K current in phase 1 of action potential leads to a more negative potential, which inactivates inward I_{Ca} current.[3,32] The consequence is the heterogeneous loss of the action

potential dome, shortening of action potential, and a transmural and transepicardial repolarization dispersion. In the next step, propagation of the action potential dome from normal regions to affect regions results in phase 2 reentry and a short coupled extra systole on the previous T wave (R on T phenomenon) that may initiate a VA.[1,3] The depolarization hypothesis indicates that fibrosis-related slow conduction in the right ventricular outflow tract (RVOT) results in discontinuous conductions, late potentials, and arrhythmia.[32] The presence of late fractionated signals in the epicardium of RVOT along with evidence of fibrosis and reduced gap junctions in myocardial biopsies are suggested to support this hypothesis.[18] It is also suggested that the ablation of these slow conduction regions in RVOT is the reason for the therapeutic effects of ablation.[33]

It seems that evidence is more in favor of repolarization hypothesis. In a study on canine right ventricle, administration of a Na blocker and K_1 channel opener led to shortening of epicardial action potential and repolarization dispersion. Phase 2 reentrant premature ventricular complexes (PVC) were accentuated resulting in VA. Blocking of the I_{to} current by quinidine normalized the ST segment elevation and prevented VA.[34] Another fact for repolarization theory is the response to quinidine. If conduction delay was responsible for the response to quinidine, quinidine would worsen ECG manifestations and late potential by blocking the Na channel. By contrast, the drug can normalize ECG and late potentials by blocking the I_{to} current.[26]

Challenge test

Challenge test with sodium channel blockers is performed when there is no spontaneous type 1 Brugada ECG, but there is clinical suspicion.[3] Induction of type 1 ECG features following the administration of procainamide, ajmaline, or flecainide is considered a positive result. The test must be terminated in case of frequent PVCs or arrhythmias and QRS widening compared to baseline values. It should be mentioned that a type 1 Brugada ECG pattern in 24-hour ambulatory monitoring is considered a spontaneous type 1 ECG, and challenge test is not needed in such cases. Furthermore, the test is not performed in individuals with a documented type 1 ECG during fever. Ajmaline provocative test is used to demonstrate malignant forms of ERP. Persistence of ERP after drug administration is associated with a higher risk of arrhythmia compared to normalization of ECG.[35]

The 2017 AHA/ACC Guideline for VA has proposed a class IIa recommendation for a pharmacological challenge using a sodium channel blocker for diagnosis.[27]

Risk stratification

Most asymptomatic individuals with ERP in ECG are not at risk of VA and need further evaluation. High risk individuals include those with a history of syncope, resuscitation in cardiac arrest, documented VA, family history of sudden death, and global J waves on ECG including right precordial leads (Brugada pattern).[36,37] Furthermore, appearance of J wave in hypothermia and other cardiac diseases like acute myocardial ischemia and heart failure may be a predictor of VA and worse prognosis.[38,39]

The presence of ERP in multiple leads,[39] J point elevation ≥ 2 mm, and a horizontal or descending ST segment[40] are associated with an increased risk of arrhythmia and cardiac death. In previous studies, the prevalence of inferior ERP was significantly higher (20-30%) in individuals with aborted sudden death of unknown etiology.[41] Thus, a 1-mm J point elevation in lateral leads with an ascending ST segment carries a low risk. Other potential risk factors for VA include a short QT interval[42] and a low T/R ratio.[35] It is noteworthy that electrophysiologic study (EPS) cannot predict VA in asymptomatic patients with ERP.[35]

In BrS, clinical symptoms are the most powerful predictor of the risk of arrhythmia. The risk of recurrent VA in survivors is about 50% in 10 years.[3] The next predictor of sudden cardiac death is a history of syncope. Among asymptomatic individuals with a Brugada type ECG, spontaneous type 1 ECG is associated with a high risk of VA.[20] A family history of sudden death in the first relatives of patients increases the risk. Induction of VA in EPS of asymptomatic individuals causes discrepancy in risk estimation in different studies, but it seems that sustained VA induced by electrical stimulation may be associated with a higher risk of sudden death.[20] This led to a class IIb recommendation in the 2017 AHA/ACC Guideline for VA of an EPS in asymptomatic spontaneous type 1 BrS patients for risk stratification.[27] Other potential factors include the presence of QRS fragmentation, sinoatrial node dysfunction, T wave alternans, and ventricular refractory period of less than 200 ms.[43,44] T_{peak}-T_{end} (peak of T wave to its end) interval and T_{peak}-T_{end}/QT ratio are related to arrhythmia inducibility

and are suggested for risk estimation.[45]

Non-Pharmacological Treatment

No treatment has been postulated for patients with ERS. Non-pharmacologic lifestyle modification to reduce the risk of arrhythmia is important in BrS. Obtaining ECG and antipyretic treatment, in case of fever, and avoidance of alcohol or cocaine consumption should be considered in known patients.[3] The 2015 ESC Guideline on VA has a class I recommendation for avoidance of excessive alcohol or large meal consumption, avoidance of drugs that intensify ST-segment elevation, and treatment of fever.[28] The AHA/ACC Guideline on VA 2017 has the same recommendations, with the addition of "avoid cocaine".[27]

The 2017 AHA/ACC Guideline on VA has a class I recommendation for observation of asymptomatic patients with ERP or an inducible type 1 Brugada pattern on ECG with no intervention.[27]

ICD implantation

ICD is the only effective treatment in high risk individuals with BrS or ERS.[3] Based on the AHA/ACC Guideline on VA, ICD implantation in ERS is indicated for patients with cardiac arrest or sustained VA.[27] Symptomatic patients with type 1 Brugada ECG should be referred for ICD implantation. The above guideline has a class I recommendation for ICD implantation in patients with spontaneous type 1 Brugada ECG with cardiac arrest, sustained VA, or syncope probably due to VA.[27]

The 2015 ESC Guideline on VA[28] has 3 differences with the AHA/ACC guideline. First, it has a class IIa recommendation for ICD implantation in patients with spontaneous type 1 Brugada ECG and syncope. Second, it has a class IIb recommendation for ICD implantation in BrS developing VA during EPS. Third, there is no specific recommendation for ICD implantation in ERS. However, the 2013 expert consensus on inherited arrhythmia has the same class I recommendation for ICD implantation in ERS compared to the AHA/ACC guideline.[29] This expert consensus also has 2 class IIb recommendations for ICD implantation, first, in symptomatic family members of patient with ERS and ST segment elevation of inferior or lateral leads, and second, in asymptomatic patients with a strong family history of sudden death and a high risk ERP.[29] ICD implantation is not recommended in asymptomatic patients with ERP.

Pharmacologic therapy and radiofrequency ablation

Complications may occur following ICD implantation. First, about two-thirds of the patients will experience inappropriate shock or lead failure (especially young active men) in a 10-year period.[46] These complications may become a major problem in young children. Long life expectancy due to young age would result in repeated ICD replacements and concomitant risk of device related infections.[46] Second, ICD may not be an available choice in many regions due to financial issues. Third, frequent appropriate shocks due to recurrent VA may lead to decreased quality of life (QOL). Forth, psychologic issues should be considered regarding the anxiety of repeated hospitalizations and surgical procedures or inability to participate in competitive sports due to the younger age of patients.[47]

Considering the above limitations, different studies have evaluated various pharmacological agents in order to administer a drug as an alternative to or in combination with ICD to reduce VA recurrence. These drugs are predominantly assessed in BrS. Beta blockers and amiodarone are ineffective.[20] Class IA (procainamide, ajmaline, etc.) and IC (flecainide, propafenone) may worsen ECG manifestations and induce arrhythmia and are therefore contraindicated.[3] However, 2 class IA drugs showed different results. Dysopiramide reduced ECG manifestations or prevented VA in some patients.[48] Moreover, promising results were reported following the administration of quinidine, the only class IA antiarrhythmic drug with I_{to} blocking property. Quinidine was effective in restoring the action potential dome in the epicardium and preventing polymorphic ventricular tachycardia (VT) along with decreasing and normalizing the ST segment elevation on ECG. Thus, it can be prescribed for prolonged suppression of arrhythmia.[44,49]

Isoproterenol is another effective drug. Its efficacy is due to its increasing of the sympathetic tone, acceleration of the heart rate, and augmentation of the inward calcium current.[3,20] It is used successfully to control VF storms. This drug is also effective in VF storms in ERS.[35]

Cilostazol, a phosphodiesterase III inhibitor, has positive effects on ECG manifestation, probably due to its increasing of the calcium current and its effect on $I_{K\text{-}ATP}$. In one study, bepridil was used in

combination with cilostazol to reduce drug-induced palpitation and boost its therapeutic effects due to its I_{to} blocking properties. Individuals with BrS and ERS were included in this study. The combination of cilostazol and bepridil successfully prevented VA.[50] Treatment with bepridil alone was successful in reducing VA in individuals with BrS and SCN5A mutation, but not in other Brugada patients.[51]

Milrinone is another phosphodiesterase III inhibitor that can increase calcium current and heart rate. This drug normalized repolarization abnormalities and ECG manifestations in a canine model, but no clinical data is available.[52]

EPS guided medical therapy was evaluated in a French study. Hydroquinidine was administrated to asymptomatic Brugada patients with inducible VA. In the long-term follow-up, the rate of arrhythmic events was very low and suitable patients for drug therapy could not be selected based on EPS.[53]

Ablation of the anterior aspect of RVOT epicardium in BrS patients can normalize ST segment elevation and prevent arrhythmia.[33,54] It can particularly be effective in refractory cases with frequent appropriate ICD shocks. There is no data on left ventricular ablation in ERS.

The 2017 AHA/ACC Guideline on VA has 2 class I recommendations on the initiation of quinidine or catheter ablation in BrS, first, patients with recurrent ICD shocks due to polymorphic VT, and second, patients with spontaneous type 1 Brugada ECG and symptomatic VA who refuse ICD implantation.[27]

The 2015 ESC Guideline on VA has different recommendations on pharmacologic treatment and ablation in BrS, indicating quinidine or isoproterenol for electrical storms (IIa), quinidine for treatment of patients declining ICD implantation or for treatment of supraventricular tachycardia (IIa), and catheter ablation for patients with a history of electrical storms (IIb).[28]

The 2013 expert consensus on inherited arrhythmia is the only scientific statement recommending pharmacologic treatment in ERS. It recommends isoproterenol for treating patients with electrical storm (IIa) and quinidine for patients with ICD implantation and a history of VF (IIa).[29]

Conclusion

J wave syndrome is a rare electrical abnormality of the heart with a wide spectrum of clinical presentations. It constitutes BrS and ERS. In this contribution, we reviewed different aspects of diagnosis and management of the syndrome according to available data in literature.

Acknowledgments

None.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

RM and AR collected the initial data. AR prepared the primary draft. RM and ME reviewed the draft. RM made the revisions.

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