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The management of Brugada syndrome patients

Andrés Ricardo Pérez Riera[1], Li Zhang[2], Augusto Hiroshi Uchida[3], Edgardo Schapachnik[4], Sergio Dubner[5] and Celso Ferreira[6]

[1]Electro-Vectocardiology Sector of the Discipline of Cardiology, ABC Faculty of Medicine (FMABC), Foundation of ABC (FUABC), Santo André, São Paulo, Brazil
[2]University of Utah School of Medicine, Department of Cardiology, LDS Hospital, Intermountain Healthcare, Salt Lake City, UT, USA
[3]Electrocardiology Service of the Heart Institute, São Paulo Medical School, Brazil
[4]Department of Chagas Disease of the Dr. Cosme Argerich Hospital, Buenos Aires, Argentina
[5]Arrhythmias and Electrophysiology Service, Clinical and Maternidad Suizo Argentina, Buenos Aires, Argentina
[6]Discipline of Cardiology, School of Medicine, ABC Foundation, Santo André, São Paulo, Brazil, Federal University of São Paulo, São Paulo, Brazil

Abstract

Brugada syndrome is a congenital electrical disorder characterised by the appearance of distinctive QRST-T patterns in the right precordial leads and an increased risk of sudden death (SCD) in young healthy adults. Although chamber enlargement is not apparent in most cases, autopsy and histological investigations have revealed structural abnormalities. The typical Brugada ECG manifestation is often concealed and may be revealed by Class IC anti-arrhythmic agents with the effect of blocking the fast component of sodium channel currents. The syndrome may also be unmasked or precipitated by a febrile state, vagotonic agents, α-adrenergic agonists, β-adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin and hypokalaemia, as well as by alcohol and cocaine toxicity. Since the typical Brugada ECG pattern can be normalised by Class IA agents to block transient outward currents (I_{to}) or by isoproterenol and cilostazol to boost calcium channel currents, they have been considered pharmacological therapies aimed at rebalancing the ion channel currents during cardiac depolarisation and repolarisation. Case studies by intra-cardiac mapping-guided ablation in the right ventricular outflow tract and Purkinje network have shown evidence of eliminating the substrate of ventricular tachycardia/fibrillation (VT/VF) in Brugada syndrome, which may be used as an adjunct to device therapy to abort electrical storms. At present the most effective therapy to prevent sudden cardiac death in Brugada syndrome is an implantable cardioverter defibrillator. (Cardiol J 2007; 14: 97–106)

Key words: Brugada syndrome, quinidine, isoproterenol, implantable cardioverter defibrillator, radiofrequency ablation

Introduction

The literature to date has shown some benefit in treating Brugada syndrome in special circumstances with I_{to} channel-inhibiting drugs in phase 1 of action potential, and with drugs that stimulate

Address for correspondence: Andrés Ricardo Pérez Riera, MD
Sebastião Afonso, 885 CEP: 04417-000
Jardim Miriam, São Paulo, Brazil
Tel: (11) 5621 2390, fax: (11) 5506-0398
e-mail: riera@uol.com.br

the slow calcium channel in phase 2. In clinical practice quinidine and isoproterenol are the drugs used. We believe that the isolated use of quinidine in symptomatic Brugada syndrome requires a greater number of evidence-based medical cases. Quinidine is indicated in association with an implantable cardioverter defibrillator (ICD) to decrease the number of shocks that the device should apply. Low-dose quinidine has potential as an adjunctive therapy for Brugada syndrome patients with frequent ICD shocks. Additionally, quinidine is indicated in oral administration in electrical storms in association with the treatment of choice. These are rare and ominous events with a high rate of lethality. Isoproterenol should be immediately infused in association with cardiopulmonary bypass and general anaesthesia. If this procedure proves to be insufficient, oral quinidine should be administered. In the absence of response to the above-mentioned steps, radiofrequency ablation should be attempted. Finally, in the face of sequential failure of these resources, it is possible to apply, exceptionally and as a heroic measure, orthotopic transplantation, which has been recorded only once in the literature on Brugada syndrome.

The pharmacological alternative is of great social interest in poor third-world countries and in developing countries, where cardioverter defibrillators are unaffordable and where very small infants are involved, making implantation technically impossible.

Infusion of the β-adrenergic stimulant agent isoproterenol is the treatment of choice in an electrical storm, because it boosts the L-type calcium current [I (Ca-L)], an adjunct to aortocoronary bypass and general anaesthesia. The same mechanism of action has been proposed for a possible beneficial effect of cilostazol.

For symptomatic carriers of the syndrome with a history of syncope or aborted sudden death (secondary prevention), the implantation of ICDs is the management of choice. We believe that associated oral quinidine in low doses is indicated.

Some groups of researchers have, in a small number of cases, demonstrated that arrhythmic events may be eliminated using mapping and ventricular fibrillation ablation associated with Brugada syndrome. In spite of the promise of this form of management, it is considered to be an experimental procedure, as there is no proof of its safety in the follow-up in a significant number of patients. Currently the procedure is justified in an electrical storm after failure of an association of isoproterenol/aortocoronary bypass/general anaesthesia.

The following are analysed successively: the value of drugs, implantable cardioverter defibrillators (ICDs), treatment with implantable pacemakers (IP) in Brugada syndrome (BrS) and allelic diseases, therapy of an electrical storm (ES) and mapping and ablation of ventricular fibrillation (VF) associated with BrS.

The value of drugs agents that block the I_{to} channel

Quinidine

Quinidine is a Class IA anti-arrhythmic drug, the isomer of the quinine found in the bark of the cinchona tree. The drug affects depolarisation and repolarisation by blocking the Na^+ and K^+ channels respectively. The rapid Na^+ channel block accounts for its greater effect on depressing V_{max} at faster rates. In BrS it is used for its property of blocking the I_{to} channel and thus restoring electrical homogeneity across the ventricular myocardial wall, and also in order to eliminate arrhythmias by phase 2 re-entry. Quinidine, by virtue of its action in blocking $I_{to,}$ has been proposed as adjunctive therapy, with an ICD as backup. Additionally the drug has a beneficial vagolytic effect, which occurs through muscarinic (M_2) receptor block. The channel blocks by means of drugs and their pharmacokinetic effect on ECG and electrophysiological intervals are summarised in Table 1.

In 1987 Imaizumi and Giles [1] showed that quinidine induced inhibition of I_{to} in the cardiac muscle. Extracellular application of quinidine reduced whole-cell cloned I_{to} amplitude in a concentration-dependent manner [2].

Research from the Masonic Medical Research Laboratory has suggested a new pharmacological approach to therapy using „transient outward current" blockers. This pharmacological alternative may be critically important in many parts of the world where ICDs are not affordable [3]. Additionally, this is particularly important because BrS patients are at risk of sudden cardiac death (SCD) from the age of 6 months [4], and an ICD implant is not feasible in very young symptomatic children [5].

Belhanssen et al. [6] performed an electrophysiological (EP) study in 34 consecutive patients who had IVF with (n = 5) or without (n = 29) BrS. All patients with inducible sustained polymorphic ventricular tachycardia/ventricular fibrillation (SPVT/VF) underwent repeated EP evaluation after oral administration of quinidine. Patients rendered non-inducible received this therapy on a long-term basis. SPVT/VF was induced in 27 (79.4%) patients at baseline studies.

Table 1. Channels and receptors blocked by quinidine, pharmacokinetics of quinidine and effect on ECG and electrophysiological intervals of quinidine

Channels and receptors blocked by quinidine
Fast Na^+ current: phase 0 of action potentials
I_{to1} channel or transient outward current: phase 1
Inward rectifier I_{K1}
Delayed rectifier: I_{KS}, I_{KR} and I_{KUR}: phase 3 of action potentials
IK_{ATP} or adenosine triphosphate ATP sensitive potassium channel
IK_{-Ach}
α_1 and α_2 adrenergic receptors: can cause orthostatic hypotension and reflex sinus tachycardia
M_2 muscarinic receptor: vagolytic effect
Pharmacokinetics of quinidine
Bioavailability: 70–85%
Protein binding: 70–95% with α_1 glycoprotein
Time-to-peak concentration: 1–4 h
Elimination $T_{1/2}$: 6 h or 8 h
Therapeutic range: 2–5 μg/ml
Elimination route: hepatic through the cytochrome P450 system
Effects on ECG and electrophysiological intervals of quinidine
Sinus coronary level: > or 0
PR interval: 0
QRS interval: >+
QT/QTc interval: >++
JT interval: >++
AH interval: <+
HV interval: >+
Atrium effective refractory period: >+
Atrioventricular node effective refractory period: >+
His-Purkinje system effective refractory period: >+
Ventricle effective refractory period: >+
Accessory pathway effective refractory period: >+

Quinidine effectively prevented induction of SPVT/VF in 26 (96%) patients. Of the 23 patients treated with these medications no patient died or had a SPVT during a mean follow-up period of 9.1 ± 5.6 years (7 to 20 years in 15 patients). Two deaths occurred in patients without inducible SPVT/VF at baseline studies who had been treated empirically. This result suggests that EP-guided therapy with quinidine is a reasonable, safe and effective approach for the long-term management of patients.

Publications have shown a decrease or disappearance of ST elevation in right precordial leads with administration of quinidine by decreasing the initial outflow of potassium through the I_{to} channel [7, 8]. The drug also suppresses all ambient unifocal premature ventricular contractions (PVCs) and induction of VF on programmed electrical stimulation. Additionally, it could improve repolarisation as a result of its vagolytic effect (M_2 muscarinic receptor block) and the exacerbation of reflex sympathetic tone. Hydroquinidine therapy prevented VT/VF inducibility in 76% of asymptomatic patients with BrS inducible arrhythmia, as well as VT/VF recurrence in all BrS patients with multiple ICD shocks. These data suggest that preventive treatment with this drug may be an alternative strategy to ICD placement in asymptomatic patients with BrS and inducible arrhythmia [9].

At a dose of oral 1000 mg to 1500 mg/day (300 mg every 6 h) [10] quinidine bisulphate can be successful in the suppression of an ES.

The management of patients with BrS is still far from well defined. Interestingly, in some reports hydroquinidine has been shown to reduce the incidence of spontaneous ventricular tachycardia in the follow-up as well as the frequency of VT/VF induced in the EP lab. Yet prophylactic ICD implantation remains the treatment of choice in symptomatic and inducible patients [11].

For ES quinidine could be effective in halting new ominous events [12]. Quinidine may be regarded as an adjunctive therapy for patients at higher risk and may reduce the number of cases of ICD shock in patients with multiple recurrences [13].

The electrical storm is a rare but malignant and potentially lethal event. Isoproterenol should immediately be infused in association with bypass and general anaesthesia, while oral quinidine should be further administered when these procedures are not effective. In the event of the failure of these therapeutic options ablation of the triggering ventricular ectopies should be attempted [14].

Recently Probst et al. [15] have attempted successfully to use hydroquinidine in the 16-month follow-up of a 3-year-old child, a carrier of BrS, who had had repetitive episodes of monomorphic ventricular tachycardia.

Watanabe et al. [16] showed in a study conducted in 8 BrS carrier patients that the beneficial effect of quinidine that decreases ST-segment elevation in the right precordial leads is more marked in those patients with a greater degree of elevation in baseline ECG and that the drug may possibly increase ST-segment elevation in some BrS carrier patients (a paradoxical effect).

Tedisamil

Tedisamil dihydrochloride is an experimental drug that exerts anti-ischaemic and anti-arrhythmic effects by the blockade of the cellular cardiac repolarisation K^+ currents as well as of multiple neuronal and vascular K^+ currents (I_{to}, Ik, and K^+_{ATP}). I_{to} blockers may be more potent than quinidine because of the lack of the relatively strong inward current blocking actions of quinidine. The development of a cardioselective and I_{to}-specific blocker is necessary in addition to the limited therapeutic armamentarium currently available to combat this disease. Appropriate clinical trials are needed to establish the effectiveness of all the above pharmacological agents. Cardioselective and I_{to}-specific blockers are not currently available commercially.

Tedisamil is a bradycardiac agent [17] that prolongs the QT interval of ECG. Drug-induced prolongation of the interval between the peak and end of the T wave (QTa-e) is reverse rate-dependent and is associated with the occurrence of a *torsades de pointes* rate and potassium. Tedisamil might be expected to have pro-arrhythmic actions similar to Class III anti-arrhythmic drugs [18].

Cilostazol

Tsuchiya et al. [19] reported a case of 67-year-old man with BrS, in whom daily episodes of VF occurred early in the morning for four consecutive days. The episodes of VF were completely prevented by an oral administration of cilostazol (Cebralat® Libbs, Pletal®). However, a recent publication has shown cilostazol to be ineffective in BrS carrier patients [20].

The drug is a quinolinone derivative that inhibits cellular phosphodiesterase type III (PDE III inhibitor). This effect was confirmed by the on-and-off challenge test, in which discontinuation of the drug resulted in recurrence of VF and resumption of the drug again prevented VF. This effect may be related to the suppression of I_{to} activity secondary to the increase in heart rate and/or to an increase in L-type calcium current [I (Ca)] because of an elevation of intracellular cyclic AMP concentration via inhibition of phosphodiesterase activity. The drug might have an anti-VF potential in patients with BrS. Concomitant administration of quinidine with a single dose of cilostazol 100 mg did not alter cilostazol pharmacokinetics. The two drugs in association in patients with BrS could theoretically have more strength in inhibiting the I_{to} channel and eliminating arrhythmias by phase 2 re-entry.

Oral denopamine, atropine or cilostazol all increase I_{Ca2+-L}, and for this reason may be effective in reducing episodes of VF.

Cilostazol is indicated in clinical practice for intermittent claudication, because it affects both vascular beds and cardiovascular function. It produces non-homogeneous dilation of the vascular beds, with greater dilation in the femoral beds than in the vertebral, carotid, or superior mesenteric arteries. The renal arteries have not been responsive to the effects of cilostazol.

Adrenergic agents

The infusion of isoproterenol, a β-adrenergic stimulant, strongly augments L-type calcium current [I(Ca-L)] and is the first choice for suppressing ES associated with BrS [21]. Isoproterenol can improve ventricular repolarisation, decreases elevation of the J point and ST segment and normalises ECG in BrS [22]. The administration of isoproterenol associated with general anaesthesia and cardiopulmonary "bypass" is effective in diminishing ST-elevation in the right precordial leads, disappearance of short-coupled premature beats and removing ES crises of VF [23–28].

ST elevation in V1-V3 was decreased by 1 mm or more after isoproterenol infusion in 8 of 11 cases of BrS. In a ventricular activation isochronal map of the body surface delayed conduction was noted on the upper anterior chest in 11 and on the anterior left chest in 2. Delayed conduction areas were decreased by isoproterenol. A QRST isointegral map showed normal findings in baseline with minimal changes after isoproterenol. An activation recovery interval (ARI) isochronal map was reduced by isoproterenol. Activation recovery interval dispersion (ARI-d), defined as the difference between the maximum and minimum values of the ARI, was decreased after isoproterenol [29]. The late potential from signal-averaged electrocardiography during isoproterenol infusion in patients with BrS was tested by Takagi et al. [30]. The subjects were 11 patients with BrS and 6 healthy individuals. In all subjects the total filtered QRS duration (fQRS), the root mean square voltage of the 40 ms terminal portion of the QRS [RMS(40)], of the low amplitude electrical potential component (40 μV) of the terminal portion of the QRS [LAS(40)] and the duration of the fQRS-LAS(40) difference were compared when isoproterenol was prescribed and when it was not. During isoproterenol infusion an unusual response, which resulted in LAS(40) prolongation, was observed in the patients with BrS. With isoproterenol infusion the fQRS remained unchanged, but the RMS(40) and the fQRS-LAS(40) decreased. Consequently another 3 patients with a positive late potential were diagnosed using the accepted standard

because of the administration of isoproterenol. The authors believe that the low-amplitude component was unmasked by shortening of the high-amplitude component. In patients with BrS the presence of a conduction delay in the right ventricle may be related to the occurrence of VF.

Dobutamine has been used as a pharmacological test in the identification of patients with risk, asymptomatic carriers or relatives of individuals with BrS. The test, known as the "Ajmaline and Dobutamine Test" consists of the administration of ajmaline, and later, if the patient develops the type-1 Brugada ECG pattern, he or she will receive dobutamine. If the electrocardiographic alterations disappear, the subject is considered test-positive, thus providing a basis for indicating EPS [31].

During high cardiac frequencies, the I_{to} channel becomes less prominent, which explains the decrease in ST-segment elevation and reduced ventricular arrhythmias at higher heart rates. This is a basis for indicating overdrive pacing in the prevention of VF in BrS [32].

Amiodarone

Anti-arrhythmic drugs such as amiodarone and β-blockers do not prevent SCD in symptomatic or asymptomatic individuals [33–35].

There are references to the efficacy of intravenous amiodarone in ES. Some researchers consider the use of an ICD plus amiodarone to be the treatment of choice. Adjunctive treatment with amiodarone reduced J-wave amplitude, preventing VF and decreasing the number of ICD shocks [36]. On the other hand, we do not consider amiodarone to be effective, the best association with ICD being quinidine.

Chronic amiodarone reduces the transmural dispersion of repolarisation in the heart as a result of aminopyridine duration prolongation in both the epicardium and endocardium, but there is less of a prolongation in the M region [37, 38]. Amiodarone prevents *torsade de pointes* in long QT syndrome (LQTS) by suppression of the trigger responsible for initiation or elimination of the substrate for re-entry, via a reduction in the transmural dispersion of repolarisation. *Torsade de pointes* is a form of polymorphic VT in the setting of a prolonged QT interval. Any drug, such as amiodarone, that prolongs repolarisation and hence the QT interval may cause *torsade de pointes*.

Sotalol

Sotalol may be of therapeutic benefit in patients with BrS. Glatter et al. [39] described a case of a 53-year-old man with recurrent syncopal events and a malignant family history, who was treated for 13 years with sotalol drug therapy with no further occurrence of BrS symptoms. Genetic testing revealed that he carried a BrS sodium channel SCN5A mutation (4189delT).

How is the significant clinical benefit obtained with sotalol in a patient carrier of BrS to be explained? In BrS several channels are affected:

— Primarily, the fast Na^+ one [40].
— Secondarily, the $I_{to1,}$ I_{TOA}; I_{TOF}; the $I_{TO\text{-}FAST}$ channel; the transient outward current, 4-aminopyridine (4-AP) sensitive, calcium-independent transient outward current or voltage-operated potassium channel. There are different densities of the I_{to} channel in ventricular wall thickness with many in the epicardium and few or none in the endocardium. This is the reason for the pronounced notch in phase 1, which is in the epicardium only and minimal or absent in the endocardium. Additionally, an idiopathic J wave has a different sensitivity to ischaemia and drugs in the different regions of ventricular wall thickness. Thus in the epicardium AP duration is more sensitive to K^+ concentrations and HR variations [3, 41].
— Ca^{2+} voltage-dependent channel, the independent transient outward current or $I_{Ca2+\text{-}L}$ channel. The inhibition of this channel and $I_{K\text{-}ATP}$ activation significantly contributes in BrS to transmural dispersion of repolarisation, in ST-segment elevation and also to re-entry onset in phase 2 [42].
— $I_{k\text{-}ATP}$ channel or time-independent K^+ current, activated by the fall in ATP intracellular concentration, ischaemia and hypoxia [43, 44] and inhibited by sulphonylureas such as glybenclamide [45]. Activation of an ATP-dependent potassium current can produce a marked dispersion of repolarisation and refractoriness in the epicardium as well as between the epicardium and the endocardium, leading to the development of extrasystolic activity via a mechanism referred to by Antzelevitch's team as phase 2 re-entry. The blockade of the transient outward current and/or the ATP-regulated potassium channels may be useful anti-arrhythmic interventions under ischaemic or "ATP depleted" conditions [46–48].

Sotalol is a drug made up by the racemic mixture of two isomers, D and L. The first is a β-blocking (Class II anti-arrhythmic agent) non-cardioselective component, without intrinsic sympathomimetic activity or membrane stabiliser. The L isomer has class III properties by blocking the fast outward K^+

or I_{KUR} channels at the end of phase 2 and phase 3 of aminopyridine. Thus the I_{KR} channel is the one affected in type 2 congenital LQTS (LQT2 or HERG). The drug does not affect the I_{to} channel or the I_{KUR} channel.

Many pharmacodynamic effects of sotalol remain unexplained. If the drug does not act on any of the affected channels in BrS, how is the clear clinical benefit to be explained that has been obtained with the use of this drug in keeping a 53-year-old patient free of symptoms for 13 years, a patient who had previously been highly symptomatic with recurrent syncopes and positive genetic testing for the mutation (4189delT) in the SCN5A gene (true Brugada disease)? We conjecture that the delay in repolarisation caused by the drug subsequent to inhibition of the fast outward K^+ current in the end of phases 2 and 3 of aminopyridine in turn causes a delay in the activation of the slow Ca^{2+} inward channels (I_{Ca2+-L}). The inhibition of this channel contributes to transmural dispersion of repolarisation and ST-segment elevation. Therefore the D isomer of sotalol, by causing a delay in the inactivation of the slow Ca^{2+} inward channel (I_{Ca2+-L}), fosters a decrease in ST-segment elevation, thus preventing functional re-entry being triggered in phase 2, which is the basis for polymorphic ventricular tachycardia/ventricular fibrillation bursts. Additionally, the absolute increase in intracellular Ca^{2+} is responsible for positive inotropism counterbalancing the negative inotropic and β-blocking actions, for which the L isomer is responsible.

Implantable cardioverter-defibrillator therapy in Brugada syndrome

The onset of VT/VF in BrS patients is the primary cause of SCD and thus ICD is currently the only proven effective treatment, although inappropriate shocks frequently result.

There are two circumstances which constitute indications for this.

Secondary prevention

ICDs are indicated in patients who have previously experienced syncope or who have been resuscitated from SCD. The Unexplained Cardiac Arrest Registry of Europe (UCARE) has shown that patients with sustained VT/VF run a high risk of recurrence. ICD implantation is then the treatment of choice [49].

Primary prevention: asymptomatic patients at high risk of SCD without prior arrhythmias

Only 1% to 5% of patients survive an out-of-hospital cardiac arrest, which emphasises the need for primary prevention of SCD [50].

Data from Brugada series indicate that the asymptomatic BrS patients at highest risk are males with inducible VT/VF and a spontaneously elevated ST segment (Type 1 ECG pattern). However, from the Priori and Eckardt series EPS is unnecessary and has no place in risk stratification in these patients. These studies suggest that asymptomatic patients with Brugada-type ECG who have no family history of SCD have a relatively benign clinical course [51]. Until more specific data are available the recommendation with respect to patients who manifest a spontaneous Type 1 ECG only after placement of the right precordial leads in a superior position is to treat them no differently from patients exhibiting a spontaneous Type 1 ECG with the leads in the standard positions.

The low incidence of ICD used in primary prevention patients serves to emphasise that efforts should be made to develop better instruments for risk stratification [52]. Asymptomatic patients who have no family history and who develop a Type 1 ECG only after sodium channel blockade should be closely followed up.

High-risk patients with LQTS, short QT syndrome (SQTS), hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and BrS are candidates for prophylactic ICD implantation, although questions remain regarding what constitutes high risk in these patient populations. The death rate is 0% in patients who have received ICD treatment. However, owing to the risks involved, ICD implantation in the increasingly young patient population is a very difficult clinical decision. New evidence suggests that an ICD may be effective for primary prevention of sudden death. The high instrumental cost and the potentially large number of candidates will have a significant impact on hospital budgets [53].

Treatment with implantable pacemakers in Brugada syndrome and allelic diseases

Mutations in SCN5A lead to a large spectrum of phenotypes, including LQT3, BrS, mixed forms and isolated progressive cardiac conduction defects (Lenègre disease).

Because I_{too} becomes less prominent at a faster rate, increased heart rate is associated with decreased ST-segment elevation in ECG and probably a decreased incidence of VT/VF. There is one report on the prevention of VF in a man with BrS by overdrive pacing from his dual chamber ICD [32].

Patients with isolated progressive cardiac conduction defect and syncope episode require pacemaker implantation [54, 55].

Successful treatment appears to be permanent with pacemakers, which stop the heart from slowing excessively, although this may not prevent ventricular arrhythmias. Therefore additional medical treatment with tablets or even an ICD may be appropriate.

In the LQT3 variant it has been reported that cardiac pacing in has a beneficial effect. Cardiac pacing is clearly indicated in patients with LQTS with atrioventricular block and whenever there is evidence of pause-dependent malignant arrhythmias. The pacemakers must always be used in association with β-blocking therapy. Pacemakers that control the heart rate have been used successfully, as have ICDs. These are similar to pacemakers, except they are also able to cause a shock to the heart when a rhythm disturbance occurs that might be life threatening. In addition to these measures, we advise patients with LQTS to avoid excessive exercise or strenuous athletic activities.

The implantation of a pacemaker has turned out to be an effective prevention for SCD in the LQT3 variant. These facts indicate that the mechanism of lethal tachyarrhythmias may possibly be associated with bradycardia in some cases of BrS.

Pacemaker implantation has proved to be extremely effective in patients with the 1795InsD mutation in SCN5A, which manifests combined Brugada and LQTSy phenotypes (mixed forms). We have no data that might exclude further study of the potential value of pacemaker therapy.

Therapy of an electrical storm in Brugada syndrome

Electrical storms are recurrent multiple episodes of VF or VT, 20 or more episodes per day or 4 or more per hour.

Isoproterenol improves ventricular repolarisation, and decreases elevation of the J point and ST segment and can even normalise the ECG tracings in BrS. This drug has therefore been used in treating the so-called "electrical storm". Isoproterenol is indicated in ES in association with general anaesthesia and cardiopulmonary "bypass". There are references to suppression of ES by oral quinidine [56, 57].

If isoproterenol associated with bypass and general anaesthesia and oral quinidine are ineffective in suppressing ES, radiofrequency ablation should be attempted. Finally, cardiac transplantation may be the last option for BrS patients with frequent ES who are unresponsive to all available treatment [58]. There is one case reported in the literature of a patient with BrS who required heart transplantation to control multiple ES. This took the form of recurrent ES treated with isoproterenol associated with general anaesthesia and cardiopulmonary "bypass" that did not respond and which was treated with heart orthotopic transplantation [59].

Mapping and ablation of ventricular fibrillation associated with Brugada syndrome

Until recently, the management of patients who have survived SCD has focused on treating the consequences by implantation of an ICD. However, such therapy remains restricted in many countries and is associated with a prohibitive cost to the community. The high instrumental cost and the potentially large number of candidates would have a significant impact on hospital budgets [60] and may be a cause of significant morbidity in patients with frequent episodes of ES or arrhythmia. Recurrent VT or VF followed by frequent ICD shocks might thus put patients in a painful situation.

Evidence emerging from the study of fibrillation both in the atria and the ventricle suggests an important role for triggers arising from the Purkinje network or the right ventricular outflow tract in the initiation of VF. Initial experience in patients with idiopathic ventricular fibrillation, and even those with VF associated with LQTS, BrS and genuine Idiopathic VF, suggests that long-term suppression of recurrent VF may be feasible by the elimination of these triggers. With the development of new mapping and ablation technologies and greater physician experience catheter ablation of VF, with the ultimate aim of curing such patients at risk of SCD, may not be an unrealistic goal in the future [61, 62].

Haissaguerre et al. [63] localised the earliest endocardial activity by mapping and by focal radiofrequency ablation of polymorphic ventricular tachycardia/ventricular fibrillation in three patients with BrS. The authors conclude that triggers from the Purkinje arborisation or the right ventricular outflow tract have a crucial role in initiating VF associated with BrS and LQTS. These can be eliminated by focal radiofrequency ablation.

In a highly symptomatic 18-year-old-male with BrS frequent episodes of VF, fast polymorphic ventricular tachycardia and fast sustained monomorphic ventricular tachycardia were observed. The episodes were classified as VT or VF and as a consequence received appropriate therapies with the ICD. Precipitating ventricular premature contractions (VPCs) stored in the ICD memory and on the ECG exhibited the same morphology as frequent isolated VPCs.

During the electrophysiological study right and left atrial tachycardia with one-to-one atrioventricular conduction were induced and successfully ablated. VF was ablated using the same non-contact mapping system-triggering VPCs from right ventricular outflow tract [64].

Yu at al. [65] presented a case of recurrent syncope diagnosed as recurrent VF by an implanted loop recorder. The VF was eliminated by radiofrequency ablation of the triggering ventricular premature complexes.

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