Role of pharmacotherapy in Brugada Syndrome

Review

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Brugada syndrome is a unique form of idiopathic ventricular fibrillation (VF), and is characterized by an ECG pattern with right bundle branch block (J wave), ST-segment elevation and terminal T-wave inversion in leads V1 through V3 [1,2,3,4,5,6,7,8,9,10]. It accounts for approximately 20% of all cases of sudden cardiac death in patients with structurally normal hearts and appears to be more frequent in Southeast Asia than in other regions[5]. To date, the only established therapy for preventing sudden cardiac death due to VF in this disease is an implantation of an implantable cardioverter defibrillator (ICD)[1,2,3,4]. Although there is no room for discussion regarding the excellent and uniform efficacy of ICDs for terminating VF, the effect is confined to the termination of VF, and ICDs cannot contribute to the prevention of VF. Therefore, there are some concerns regarding ICD therapy. The first is electrical storm associated with VF or polymorphic ventricular tachycardia, which is defined as frequent appropriate ICD shock deliveries for ventricular tachyarrhythmias of ≥ 3 times over 24 hours. Chalvidan et al. [10], reported a patient who suffered from incessant VF episodes (electrical storm) and became near-fatal, but subsequently fully recovered. The second is ICD related complications including lead dislodgment, inappropriate shock delivery, infection requiring ICD removal and so on [11,12,13]. The third is the indication of ICDs for infant cases of Brugada syndrome, in which the size of the ICD is too large for implantation [11,12,13]. A new therapy other than ICD implantation to overcome these concerns seems to be urgent.

Cellular mechanism

Brugada syndrome is suggested to be a primary electrical disease, and two dozen mutations of the cardiac sodium channel gene "SCN5A", which lead to a loss of the channel function, have been found in about 15-20 % of patients with Brugada syndrome, and an autosomal mode of transmission has been demonstrated [4,5,6,7,8].

The ionic and cellular basis for the ST-segment elevation in Brugada syndrome is hypothesized to be due to an outward shift in the balance of the membrane ionic currents at the end of phase 1 and phase 2 of the action potential, in which an outward current is mainly due to the activation of the transient outward current (I_{to}), and the inward current is mainly due to the activation of an inward calcium current (I_{Ca})   and an inactivating component of an inward sodium current (I_{Na}). The net outward shift of this current balance leads to a loss of the dome or phase 2 of the action potential. Such changes may affect the right ventricular epicardium

more markedly than the endocardium and produce a marked voltage gradient in the membrane potential between the end- and epi-cardial sides of the right ventricular muscle fibers during the phase 2 (a change corresponding to the characteristic ST-segment elevation in V1 through V3 in the ECGs of Brugada Syndrome[4,6,7,8].

The loss of the action potential dome in the epicardium but not in the endocardium results in the development of a marked transmural dispersion of repolarization and refractoriness, responsible for the development of a vulnerable window during which a premature impulse or extrasystole can induce a reentrant arrhythmia. Because the loss of the action potential dome in the epicardium is usually heterogeneous, it leads to the development of epicardial dispersion of repolarization and refractoriness. Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local re-excitation via a phase 2 reentry mechanism, leading to the development of a very closely coupled extrasystole, which captures the vulnerable window across the wall, thus triggering a circus movement reentry in the form of VT or VF [4,6,7,8].

In patients with Brugada syndrome, an abnormal spike-and-dome configuration of the epicardial monophasic action potentials (MAPs) obtained from the right ventricular outflow tract, may create a prominent J point elevation[14]. Furthermore, a MAP and repolarization of longer duration in the epicardium than in the endocardium, resulting from a delayed dome formation, suggests a reversal current flow during phase 3 of the action potential. The longer duration of the action potential in the epicardium may have created the typical terminal T-wave inversion observed in Brugada syndrome [14]. Antelevitch et al., [4,7,8] suggested that the arrhythmogenic substrate arises when a further shift in the balance of the current leads to a loss of the action potential dome at some epicardial sites but not others. Actually, Nagase et al.[15], reported that a delayed potential was observed in the epicardial electrogram of the right ventricular outflow tract but not others, which was considered to be the second upstroke of the epicardial action potential (epicardial echo beat) generated by local and concealed phase 2 reentry [16].

Pharmacological therapy based on the cellular mechanism

A variety of pathophysiologic conditions and pharmacologic interventions, which either increase the membrane outward currents or reduce the inward currents should produce a loss of the action potential dome in the right ventricular epicardium and facilitate the occurrence of VF. Phase 2 of the action potential could be abolished by reducing the I_{Na} as predicted by the ST-segment elevation after the application of Class IC agents and restored by increasing the inward current, e.g., by enhancing the I_{Ca} or by decreasing the outward I_{to} current, e.g., by the application of quinidine as reported [4,7,8].

There are many pharmacologic therapies that have been clinically examined. Class IC agents are clearly contraindicated because theses drugs reduce the I_{Na} as mentioned above [17]. Class IA agents, including procainamide and disopyramide, are contraindicated since these drugs strongly depress the I_{Na} but only mildly affect I_{to}, and are well known to exacerbate the ST elevation and occurrence of VF[4,7,8,9]. Class IB agents, which lack an I_{to} blocking effect and display little use-dependence owing to a rapid dissociation from the sodium channel, are not at all effective in the normalization of the ST-segment elevation [13]. Both amiodarone and beta-blockers are also shown to be ineffective[4,7,8,9].

Because the presence of a prominent I_{to} is at the heart of the mechanism underlying Brugada syndrome, any agent that blocks this current in the heart is likely to be protective [4,6,7,8]. At the time of writing this review, there was no drug developed that could cardio-selectively block the I_{to}. An isolated case report showed that DDD-pacing at a relatively high rate is effective in decreasing the I_{to} (and hence suppressing VF), possibly because the repriming time of the Ito channels is reported to be fairly long [18]. There is, however, no systematic study to examine the effect of relatively high rate pacing on the prevention of VF. Quinidine, another class IA agent, has been shown to directly inhibit Ito in addition to a secondary inhibition due to an increase in the heart rate by a vagolytic action[4,7,8]. Experimental studies have shown quinidine to be effective in restoring the epicardial action potential dome, thus normalizing the ST-segment and preventing phase 2 reentry and polymorphic VT in experimental models of Brugada syndrome [7,8].

Belhassen et al. [11], reported very important and provocative observations regarding the effect of quinidine on the prevention of VF in 34 consecutive patents with idiopathic VF, 5 of whom met the diagnostic criterion of Brugada syndrome. In the study, electrophysiologic study (EP)-guided therapy with class IA agents (mainly quinidine) was performed. These agents effectively prevented the induction of sustained polymorphic ventricular tachycardia (SPVT) and/or VF in 26 of 27 patients (96%), in all of whom SPVT or VF was induced in the baseline EP studies. Of the 23 patients treated with these medications, no patients died or had a sustained ventricular arrhythmia during a mean follow-up period of 9.1$\pm$5.6 years. They concluded that EP-guided therapy with class IA agents (mainly quinidine) was a reasonable, safe and effective approach for the long-term management of patients with idiopathic VF including Brugada syndrome. Although there have been no randomized placebo-controlled prospective studies of EP-guided quinidine therapy, I think that quinidine is a promising antiarrhythmic agent. The experimental antiarrhythmic agent, tedisamil, with its potent I_{to}, among other outward current, blocking action, has been suggested as a therapeutic candidate[8]. This drug may be more potent than quinidine because it lacks the relatively strong inward current blocking actions of quinidine.

There are, however, some limitations in using quinidine for the prevention of VF in patients with Brugada syndrome. There are some risks with antiarrhythmic agents with regard to the potential for a loss of efficacy or proarrhythmic effects under a number of conditions including hypokalemia, hypomagnesemia, bradycardia, therapy with other agents that alter repolarization, metabolic inhibitors, and changes in myocardial substrates. Furthermore, quinidine is known to have other non-cardiac side effects including abdominal cramping, diarrhea, cinchonism, which consists of decreased hearing, tinnitus, and blurred vision, thrombocytopenia, lupus syndrome, and anticholinergic side effects including a dry mouth, urinary retention and so on. These side effects may affect the compliance with the drug [11]. The anticholinergic action on the heart might contribute to the anti-VF effect of the drug by increasing the heart rate [13].

Another approach for the prevention of VF in patients with Brugada syndrome is to increase the I_{Ca} by promoting an intracellular level of cyclic-AMP. Intravenous Isoproterenol administration is especially known to be effective in suppressing ST elevation in leads V1 through V3 in Brugada syndrome patients, and to restore the action potential dome in models of this syndrome [4,7,8] and patients with Brugada syndrome [9,19], because it markedly increases the I_{Ca} secondary to an elevation in the intracellular level of cyclic-AMP.

Cilostazol, a new oral phosphodiesterase type-III inhibitor is primarily used as a strong

antiplatelet agent, but has been shown to increase the I_{Ca} and modestly increase the heart rate as well as contractile function. All these effects are secondary to an increased level of the cyclic-AMP caused by an inhibition of phosphodiesterase type-III activity, in guinea-pig ventricular myocytes and papillary muscles [20]. From these findings, it is reasonable to expect that this drug has an antiarrhythmic efficacy for preventing the VF often observed in patients with Brugada syndrome, because it increases the I_{Ca} due to inhibition of the phosphodiesterase activity in the ventricular myocytes and decreases the Ito due to an increased heart rate which again is secondary to an increased I_{Ca} in the sinus node. I recently presented a case of a 67-year-old man with Brugada syndrome, in whom daily episodes of ventricular fibrillation occurred early in the morning for 4 days straight and the VF was completely prevented by an oral administration of cilostazol [21]. This effect was confirmed by the on-and-off challenge test, in which the discontinuation of this drug resulted in recurrence of VF, and the resumption of this drug again prevented the VF. This effect may be related to the suppression of the Ito secondary to an increase in the heart rate and/or increase in the Ica due to an elevation in the intracellular cyclic-AMP concentration via inhibition of phosphodiesterase activity. I performed a long-term follow-up with cilostazol in three patients (the follow-up periods were 12, 26 and 32 months, respectively), and in all an ICD was implanted for the termination of spontaneous VF. In all the patients several VF episodes were observed over a one year period prior to the cilostazol, no VF was recorded by the ICD memory and the patients were free from symptoms under 100-200 mg/day of cilostazol. Further study is needed to examine the effectiveness of the drug.

Practical way to use anti-VF drugs

In patients who undergo aborted sudden cardiac death or syncope of unknown origin (symptomatic Brugada syndrome), no one argues that the implantation of an ICD is the first-line therapy regardless of the findings of the EP study. For those patients, drug therapy plays not a contradictory but a complimentary role to the ICD by reducing the number of ICD shock deliveries. Prevention of VF contributes to the improvement in the quality of life of the patients by avoiding uncomfortable ICD shock deliveries.

As mentioned above, Belhassen et al. [11], performed EP-guided medical therapy in 34 patients with idiopathic VF, in 5 of whom the criterion of Brugada syndrome were fulfilled, and reported excellent long-term results. Although medical therapy requires markers that can accurately predict the preventive effect of VF over a long-term period, there, however, seems to be no reliable marker. An EP study is usually used to examine the preventive effects of antiarrhythmic agents on sustained ventricular tachycardia in patients with structural heart disease, whereas the prognostic value of the EP study in predicting life-threatening events in Brugada syndrome is still controversial. Brugada et al., [3] suggested that among the asymptomatic patients, the inducibility of VT during the EP study might be a prognostic marker of risk. Studies by Priori et al., [22] and Kanda et al., [23] failed to find an association between the inducibility and recurrence of VT/VF in patients with Brugada syndrome regardless of whether it was symptomatic or asymptomatic. As Belhassen suggested [13], the difference might be due to the VF induction protocol in the EP study, in which Belhassen et al., used a stimulus current intensity of five times the diastolic threshold along with the use of repetition of double and triple extrastimulation at the shortest coupling intervals that resulted in ventricular capture. Further appropriate clinical trials are needed to clarify this issue.

In patients with asymptomatic Brugada syndrome who are family members of

symptomatic Brugada syndrome patients, the same strategy as that for the symptomatic Brugada syndrome patients should be considered [2,3,4]. In another asymptomatic-patient group in whom an ECG that discloses the Brugada sign is performed for routine reasons such as a workup prior to surgery or sport license or screening for insurance, risk stratification to find the patients at high risk is needed because in most cases these patients have a benign prognosis[3,22,23]. Antzelevitch et al. [4], recommended that all asymptomatic patients with the Brugada sign should undergo an EP study for risk stratification, and, if inducible, an ICD should be implanted since Brugada et al.[3], reported that an overall 8% life-threatening event rate was found in initially asymptomatic patients. Belhassen et al.,[13] suggested that EP study-guided quinidine therapy might become an alternative to ICD therapy for prophylaxis of arrhythmic events in these patients. Further appropriate clinical trials are needed.

References

1. Brugada P, Brugada J: Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. J Am Coll Cardiol 1992;20:1391-1396.

2. Brugada J, Brugada R, Brugada P: right bundle branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. Circulation 1998;97:457-460

3. Brugada J, Brugada R, Antzelevitch C, Towbin JA, Nademanee K, Brugada P:Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 2002;105:73-78.

4. Antzelevitch C, Brugada P, Brugada J, Brugada R, Towbin JA, Nademanee K: Brugada syndrome:1992-2002 a historical review. J Am Coll Cardiol 2003;41:1665-1671.

5. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Oritz-Lopes R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-Bahr E, Keating MT, Towbin JA, Wang Q: Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature 1998;392:293-296

6. Priori SG, Napolitano C, Gasparini M, Pappone C, Bella PD, Brignole M, Giordano U, Giovannini T, Menozzi C, Bloise R, Crotti L, Terreni L, Schwartz PJ: Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: a prospective evaluation of 52 families. Circulation 2000;102:2509-2515

7. Yan GX, Antzelevitch C: Celluar basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999;100:1660-1666

8. Antzelevitch C: The Brugada syndrome: ionic basis and arrhythmia mechanisms. J Caradivasc Electrophysiol 2001;12:268-272

9. Miyazaki T, Mitamura H, Hiyoshi S, Soejima K, Aizawa Y, Ogawa S: Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. J Am Coll Cardiol 1996;27:1061-1070

10. Chalvidan T, Deharo JC, Dieuzaide P, et al.: Near fatal electrical storm in apatient equipped with an implantable cardioverter-defibrillator for Brugada syndrome. PACE 2000;23:410-412

11. Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Elder M: Effects of electrophysiologic-guided therapy with class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol 1999;10:1301-1312

12. Ruskin JN: Idiopathic ventricular fibrillation: is there a role for electrophysiologic-guided antiarrhythmic drug therapy? J Cardiovasc Electrophysiol 1999;10:1313-1315

13. Belhassen B, Viskin S, Antzelevitch C: The Brugada syndrome: is implantable cardioverter defibrillator the only therapeutic option? PACE 2002;25:1634-1640

14. Kurita T, Shimizu W, Inagaki M, et al: The electrophysiologic mechanism of ST-segment elevation in Brugada syndrome. J Am Coll Cardiol 2002;40:330-334

15. Nagase S, Kusano KF, Morita H, et al: Epicardial electrogram at the right ventricular outflow tract in patients with Brugada syndrome using epicardial lead. J Am Coll Cardiol 2002;39:1992-1995

16. Antzelevitch C: Late potentials and the Brugada syndrome. J Am Coll Cardiol 2002;39:1996-1999

17. Shimizu W, Antzelevitch C, Suyama K, Kurita T, Taguchi A, Aihara N, Takaki H, Sunagawa K, Kamakura S: Effect of sodium channel blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. J Cardiovasc Electrophysiol 2000;11:1320-1329

18. Lee KL, Lau CP, Tse HF, Wan SH, Fan K: Prevention of ventricular fibrillation by pacing in a man with Brugada syndrome. J Caradivasc Electrophysiol 2000;11:935-937.

19. Tanaka H, Kinoshita O, Uchikawa S, et al: Successful prevention of recurrent ventricular fibrillation by intravenous Isoproterenol in a patient with Brugada syndrome. PACE 2001;24:1293-1294

20. Matsui K, Kiyosue T, Wang J-C, Dohi K, Arita M: Effects of pimopendan on the L-type Ca2+ current and developed tension in guinea-pig ventricular myocytes and papillary muscle: Comparison with IBMX, milrinone and cilostazol. Cardiovasc Drugs Ther 1999;13:105-113

21. Tsuchiya T, Ashikaga K, Honda T, Arita M: Prevention of ventricular fibrillation by cilostazol, an oral phosphodiesterase inhibitor, in a patient with Brugada syndrome. J Cardiovasc Electrophysiol 2002;13:698-671

22. Priori SG, Napolitano C, Gasparini M, et al: Natural history of Brugada syndrome: insights for risk stratification and management. Circulation 2002;105:1342-1347

23. Kanda M, Shimizu W, Matsuo K, et al: Electrophysiologic characteristics and implications

of induced ventricular fibrillation in symptomatic patients with Brugada syndrome. J Am Coll Cardiol 2002;39:1799-1805