normal aortic diameter have similar aortic dimensions. Patients with BAV and aortic dilatation have endothelial dysfunction as opposed to patients with BAV and normal aortic dimensions [7]. Based on this and Biner et al.'s data [6], FDRs of BAV individuals with aortic dilatation may have an increased risk of aortic dilatation due to endothelial dysfunction inheritance. We consider that our findings enriches Biner et al.'s and should prompt new studies addressed to answer the following question, "Are all tricuspid FDRs of BAV individuals at increased risk of aortic dilatation or is this risk higher only in FDRs of BAV individuals with dilated aortic dimensions?". Results from these studies should guide clinicians if it is necessary to do un-restricted screening of aortic dilatation in all FDRs of BAV individuals or if resources should be aimed at a specific high-risk profile of FDRs.

References

[1] Tzemos N, Therrien J, Yip J, et al. Outcomes in adults with bicuspid aortic valves. JAMA 2008;300:1317–25.
[2] Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. J Am Coll Cardiol 2010;55:e27–e129.
[3] Dayan V, Cura L, Muñoz L, Areco D, Ferreiro A, Pizzano N. Risk of subsequent aortic dilatation is low in patients with bicuspid aortic valve and normal aortic root diameter at the time of aortic valve replacement. Interact Cardiovasc Thorac Surg 2010;10:535–8.
[4] Abdulkareem N, Soppa G, Jones S, Valencia O, Smelt J, Jahangiri M. Dilatation of the remaining aorta after aortic valve or aortic root replacement in patients with bicuspid aortic valve: a 5-year follow-up. Ann Thorac Surg 2013;96:43–9.
[5] Cripe L, Andelfinger G, Martin LJ, Shooner K, Benson DW. Bicuspid aortic valve is heritable. J Am Coll Cardiol 2004;44:138–43.
[6] Biner S, Rafique AM, Ray I, Cuk O, Siegel RJ, Tolstrup K. Aortopathy is prevalent in relatives of bicuspid aortic valve patients. J Am Coll Cardiol 2009;53:2288–95.
[7] Tzemos N, Lyseggen E, Silversides C, et al. Endothelial function, carotid-femoral stiffness, and plasma matrix metalloproteinase-2 in men with bicuspid aortic valve and dilated aorta. J Am Coll Cardiol 2010;55:660–8.

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Efficacy of bepridil to prevent ventricular fibrillation in severe form of early repolarization syndrome

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Early repolarization is a common electrocardiographic finding, which occurs in 1% to 10% of healthy persons, and it has been generally considered benign for decades. However, there is increasing evidence showing that early repolarization is associated with an increased risk of ventricular fibrillation and sudden cardiac death, and idiopathic ventricular fibrillation associated with early repolarization, the so-called early repolarization or J-wave syndrome, started receiving increasing attention [1].

Implantable cardioverter defibrillator is the only proven effective treatment to prevent sudden cardiac death in patients with early repolarization syndrome. However, the frequency of arrhythmia recurrences is not rare. In our and other studies, 27% of patients with early repolarization syndrome develop multiple episodes of ventricular fibrillation, and 13% to 17% of patients have electrical storm defined as 3 or more episodes of ventricular fibrillation during 24 h [2,3]. Additional antiarrhythmic therapy is required to reduce defibrillator shocks and to prevent life-threatening events by

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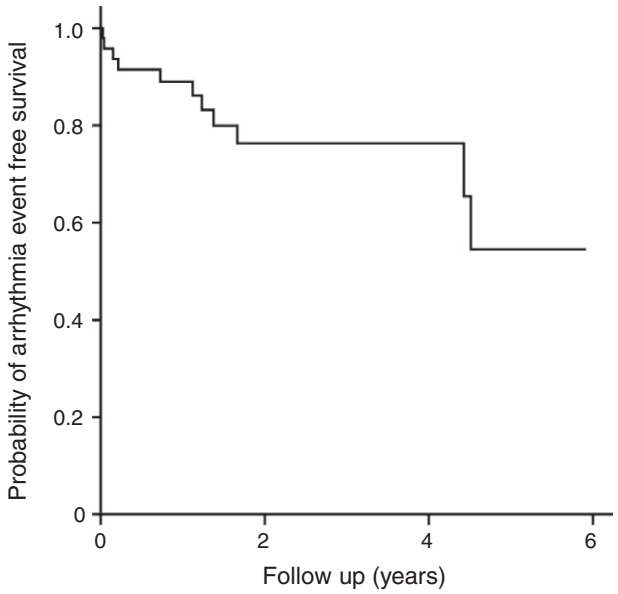

Fig. 1. Probability of arrhythmia event free survival. Ventricular fibrillation recurred in 11 of 50 patients (22%) (Incidence, 4.8 per 100 person-years [95% confidence interval, 2.0–7.6]).

electrical storm, but antiarrhythmic drugs including β-blockers, verapamil, amiodarone, and majority of sodium channel blockers have poorly been effective [2]. Although only quinidine has been effective in preventing recurrent episodes of ventricular fibrillation in patients with early repolarization syndrome, up to one third of patients cannot tolerate quinidine because of side-effects, mainly gastrointestinal ones [2,4].

Brugada syndrome is another form of idiopathic ventricular fibrillation associated with J-point elevation, and early repolarization syndrome and Brugada syndrome share genetic backgrounds, clinical characteristics, and response to pharmacological therapies such as quinidine and isoproterenol [5,6]. In some case reports, multi-channel blocker bepridil has been effective in preventing ventricular fibrillation in patients with Brugada syndrome [7,8]. Here, we describe the efficacy of bepridil in patients with early repolarization syndrome.

This study included 50 patients with early repolarization syndrome who were followed >3months after an initial event associated with ventricular fibrillation (age, 44 ± 16 years; 6 women, 11%). All patients had events associated with ventricular fibrillation, and 16 patients (29%) also had atrial fibrillation. Sodium channel blocker challenge was negative for diagnosis of Brugada syndrome in all patients. During a followup of 3.5 ± 3.4 years, arrhythmia recurred in 11 of 50 patients (22%) (incidence, 4.8 per 100 person-years [95% confidence interval, 2.0–7.6])(Fig. 1). Bepridil was administered in three patients who had multiple recurrences including two patients who had repetitive arrhythmia episodes within a short-time, so called "electrical storm", and was effective to control ventricular fibrillation. Notably, prior to bepridil, quinidine and isoproterenol failed to control arrhythmias in one of the three patients. Quinidine was discontinued due to gastrointestinal side effects in another patient (Fig. 2) (Table 1). Bepridil prolonged QT interval, but did not augment early repolarization pattern in any of the patients. In three patients in whom bepridil combined with intravenous administration of isoproterenol was effective as acute treatment, the drug was continued after discontinuation of isoproterenol. There was no arrhythmia recurrence in two patients during 3.8 years and 8 months, respectively. In the remaining patient, bepridil dramatically decreased the frequency of ventricular fibrillation, and after addition of cilostazol, there was no recurrence of the arrhythmia. Furthermore, bepridil was also effective in preventing atrial fibrillation in another patient.

Among other antiarrhythmic drugs, disopylamide was effective in preventing ventricular fibrillation during 10.2 years in one patient who had been suffered from electrical storm. Lidocaine (n = 5), procainamide (n = 4), mexiletine (n = 3), flecainide (n = 1), propafenone (n = 1), nifekalant (n = 3), amiodarone (n = 2), and sotalol (n = 1) were not effective for recurrences of arrhythmias.

We found that bepridil was effective in patients with severe form of early repolarization syndrome. A transmural differences in action potential notch has been shown as the basis of J-point elevation and ventricular fibrillation, and transient outward potassium current (Ito) blockers reduce the action potential differences resulting in decrease of J point elevation and prevention of arrhythmias in experimental models, although the precise mechanism is unclear [5]. Quinidine, which blocks Ito, has been effective for ventricular fibrillation in patients with early repolarization syndrome [2]. Bepridil is a multi-channel blocker, which inhibits sodium channel, L-type calcium channel, and multiple potassium channels. Bepridil prevented ventricular fibrillation, possibly by Ito block, although bepridil did not normalize J point elevation. Relatively short QT interval may be associated with arrhythmogenic substrate in patients with early repolarization, and bepridil prolonged QT interval in patients with early repolarization in this study, similar to those with Brugada syndrome and idiopathic ventricular fibrillation in a previous study [1,9,10]. However, nifekalant, sotalol, and amiodarone, all of which block delayed rectifier potassium current (IKr) and prolong QT interval were not effective in this and previous studies, further supporting the importance of Ito block for prevention of ventricular fibrillation [2].

Early repolarization syndrome and Brugada syndrome share responses to antiarrhythmic drugs, and this and previous studies have shown that antiarrhythmic drugs with Ito blocking property including quinidine, bepridil, and disopylamide are effective in both diseases [5,6,8,11]. The arrhythmogenicity of vagal stimulation has been reported in Brugada syndrome and early repolarization syndrome, and disopylamide may prevent ventricular fibrillation by muscarine block, in addition to Ito block [5,6]. In both diseases, atrial fibrillation is common complication with the prevalence of ~20%, but most of sodium channel blockers that are widely used for atrial fibrillation are proarrhythmic [6]. Antiarrhythmic drugs with Ito blocking property may be able to use for atrial fibrillation in early repolarization syndrome, and actually, bepridil was safety and was effective in preventing atrial fibrillation in this study.

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References

[1] Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016–23.
[2] Haissaguerre M, Sacher F, Nogami A, et al. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. J Am Coll Cardiol 2009;53:612–9.
[3] Watanabe H, Nogami A, Ohkubo K, et al. Clinical characteristics and risk of arrhythmia recurrences in patients with idiopathic ventricular fibrillation associated with early repolarization. Int J Cardiol 2012;159:238–40.
[4] Veerakul G, Nademanee K. Brugada syndrome. Circ J 2012;76:2713–22.
[5] Antzelevitch C. Genetic, molecular and cellular mechanisms underlying the J wave syndromes. Circ J 2012;76:1054–65.
[6] Watanabe H, Minamino T. Similarities and differences of clinical characteristics between Brugada syndrome and early repolarization syndrome. J Arrhythm 2013;29:134–7.
[7] Sugao M, Fujiki A, Nishida K, et al. Repolarization dynamics in patients with idiopathic ventricular fibrillation: pharmacological therapy with bepridil and disopyramide. J Cardiovasc Pharmacol 2005;45:545–9.
[8] Ohgo T, Okamura H, Noda T, et al. Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. Heart Rhythm 2007;4:695–700.
[9] Watanabe H, Nogami A, Ohkubo K, et al. Electrocardiographic characteristics and scn5a mutations in idiopathic ventricular fibrillation associated with early repolarization. Circ Arrhythm Electrophysiol 2011;4:874–81.