

## Sudden Death and Ventricular Preexcitation: Is it Necessary to Treat the Asymptomatic Patients?

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**Abstract:** Currently, asymptomatic ventricular preexcitation, which has been put at rest for many decades, remains a clinical challenge as there are no predictors of sudden death, which can be the first clinical presentation of the syndrome. Identification of risk factors for sudden death is important, considering the availability of a definitive treatment. Now, as radiofrequency catheter ablation of accessory pathways has reported success rates approaching 100 percent without major complications in many centers worldwide, it becomes unacceptable that even one asymptomatic individual with WPW will die or will experience life-threatening arrhythmic events. In our extensive experience a short anterograde refractory period of accessory pathways, inducibility of sustained tachyarrhythmias and the presence of multiple accessory pathways are the strongest predictors of life-threatening arrhythmias and sudden death. Therefore, it is not yet justified that, after an incidental diagnosis of WPW syndrome has been made, no risk stratification by invasive testing is done. Subjects at high risk, particularly if young or adolescent, should be identified and then ablated in the same session as they can develop lethal arrhythmic events within a few years and this is our current practice. Recently, we sent a questionnaire to investigate clinical practices over a large number of centers around the world about asymptomatic ventricular preexcitation. A total of 100 replies were received and the results demonstrate that there is worldwide agreement in performing invasive electrophysiologic testing and prophylactic ablation in selected subjects.

These findings provide strong evidence to revisit current guidelines, which appropriately in the absence of evidence had been conservative.

**Key Words:** Wolff-Parkinson-White, ventricular preexcitation, sudden death, radiofrequency catheter ablation.

### INTRODUCTION

Since they were first described, preexcitation syndromes have intrigued physicians and many electrophysiologic and population based studies have been reported in the past years [1-48]. Recently we have reported additional data which have animated many debates on a critical question that was thought to have been put to rest [40-44]. If one considers that in the late 1980s surgical ablation of AP was the last resort for prevention of sudden death, it is not surprising that approaches to the initially asymptomatic Wolff-Parkinson-White remained conservative. Nowadays, with the establishment of RF catheter ablation as a safe and very effective approach for treatment of symptomatic patients with Wolff-Parkinson-White syndrome, attention has turned to subjects who are asymptomatic but are known to have substrates for potentially life-threatening arrhythmias. At present, it has become unacceptable that even one asymptomatic individual with Wolff-Parkinson-White continues to die unexpectedly or to experience life-threatening arrhythmic events.

### NATURAL HISTORY OF THE WPW SYNDROME

Natural history studies of the WPW syndrome reported SD rates between 0.0% and 0.6% per year, but many of them had small numbers and limited follow-up periods. In the Munger *et al.* [6] study, no symptoms developed during follow-up in any individual >40 years of age who was asymptomatic at diagnosis, and up to 33% of asymptomatic people lost the capacity to conduct anterogradely. In contrast, a third of those <40 years of age became symptomatic. Leitch *et al.* [26] reported no cases of SD in a group of 75 initially asymptomatic subjects followed up for a mean of 4.3 years. Fitzsimmons *et al.* [23] reported that among asymptomatic military aviators with WPW, 28 of 187 (15.3%) had supraventricular tachycardia (SVT) during long-term follow-up, but among those with continuous pre-excitation, 23% experienced SVT. Munger

*et al.* [6] reported that 30% of asymptomatic patients presented with arrhythmic events over a 12-year follow-up period and 2 symptomatic patients experienced sudden death over 1338 patient-years of follow-up.

Kitada *et al.* [45] among 397 responding school children, found that those with WPW syndrome had only a fair prognosis in terms of repeated arrhythmic events rather than mortality or serious cardiovascular complications. Other studies reported lower rates of symptoms (up to 8%) with variable follow-up periods suggesting that the period of follow-up is important since some subjects may become symptomatic even after many years and may have SD as their first presenting symptom. Among 241 relatively unselected WPW patients, Pietersen *et al.* [46] identified 26 who had developed atrial fibrillation (AF). Over a mean of 15 years (range, 1 to 37 years) of follow-up, 2 of these 26 patients died suddenly. Their shortest RR intervals during induced AF had been short. In contrast, 2 of the remaining 215 patients (ie, those in whom AF did not occur) died suddenly, but this difference was not statistically significant. These findings indicate that ventricular pre-excitation is not such a benign condition as previously supposed; 4 cases of sudden death from a total of 241 WPW patients represent a 2% mortality over the follow-up period.

The results of the 3 largest published series of WPW patients who had VF demonstrated that VF was the first presentation in 3 of 25 patients, 8 of 15 patients, and 6 of 23 patients. Klein *et al.* [8] documented VF in 3 pediatric asymptomatic patients with WPW. Timmermans *et al.* reported that 15 of 690 patients (2.2%) with WPW syndrome who were referred to their hospital over a 16-year period had an aborted SD, and VF was the first clinical manifestation in 8 patients. Montoya *et al.* [9] reported 23 cases of WPW with spontaneous VF in whom VF was the first manifestation of the syndrome in 6 patients. No differences were found between those with VF and without VF. From these data, it seems that aborted SD and SD occur more frequently in young, healthy male subjects and that VF is a rare initial presentation in patients >30 years of age. We documented VF in 7 healthy, young patients (6 male patients); 5 were successfully resuscitated, and 2 died suddenly.

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Subjects who experienced VF had clinically silent life-threatening tachyarrhythmias, but they refused prophylactic RF ablation being totally asymptomatic. Two of them (1 child) died suddenly, and the others underwent ablation after cardiac arrest.

Russel *et al.* [13] reported 256 pediatric patients, 6 of whom had presented with life-threatening events as the first manifestation of their pre-excitation syndrome. Among these 256 patients, 60 (23.4%) were asymptomatic. Deal *et al.* [14] described 42 patients with WPW syndrome who experienced cardiac arrest of whom 20 as the initial symptom. Dubin *et al.* [47] reported on 100 pediatric patients with WPW syndrome who underwent EPT for risk stratification and demonstrated that asymptomatic patients had statistically the same recognized EPT risk profile as the symptomatic patients.

Bromberg *et al.* [48] reported that among 60 patients who had surgical ablation of the AP, 10 children experienced cardiac arrest. In a 15-year follow-up study, of 98 asymptomatic WPW children, 1 child 8 years of age whose parents refused to perform EPT had SD. In our experience, the incidences of VF, SD, and life-threatening syncope arrhythmias were 0.3%, 0.1%, and 1.3% per year, respectively.

### Mechanisms of Sudden Death

The most important mechanism of SD in WPW is the onset of AV reciprocating tachycardia (AVRT), which can degenerate into AF and then into VF. The possibility to conduct rapidly over a single or multiple accessory pathways (AP) with short refractory periods may facilitate degeneration of AF into VF and SD, particularly when ventricular rates exceed 300 bpm. In our experience, subjects who had VF exhibited rapid conduction with short refractory periods of both the AV node and AP as well as inducible AVRT triggering AF. The presence of multiple pathways has an important role in precipitating VF. It seems that inducibility of AVRT and multiple AP, convey an increased risk of VF or SD. Patients who were resuscitated after VF have experienced (1) clinical AF with rapid ventricular rates, (2) clinical SVT, (3) inducible AVRT or AF with rapid ventricular response or both, (4) an anterograde AP refractory period <270 ms, and/or (5) multiple pathways. These findings confirm our experience and the role of EPT in evaluating inducibility, number and location of APs, and the electrophysiologic characteristics of the bypass tracts to select high-risk patients.

### PROPHYLACTIC ABLATION IN HIGH-RISK ASYMPTOMATIC WPW PATIENTS

We reported the usefulness of prophylactic RF ablation in high-risk asymptomatic WPW subjects in 2 randomized studies published in the *New England Journal of Medicine* [41,42]. In the first study, among 220 asymptomatic patients referred to our laboratory ( $\geq 12$  years of age), 37 high-risk subjects were randomized to prophylactic ablation, and 35 received no treatment. Ablation was successful in all patients without any complications. The 5-year Kaplan-Meier curves of the cumulative probability of arrhythmic events were 7% among patients who underwent prophylactic ablation and 77% among subjects who did not. In this study, one patient with multiple pathways randomized to the conservative arm subsequently had a VF arrest, suggesting that ablation of multiple pathways is important to prevent VF and SD. All arrhythmic events occurred within the first 2.5 years of follow-up in patients with inducible AVRT, whereas more than half of those with inducible nonsustained AF remained asymptomatic at 5 years. We found that the risk of spontaneous arrhythmias significantly and persistently decreased over time after ablation. The cumulative probability to develop arrhythmic events for ablated patients and those who did not undergo ablation, continued to diverge over time, suggesting a long-term benefit. In the second study, RF catheter ablation of AP was compared with no treatment in 165 asymptomatic high-risk children 5 to 12 years of age. One of 20 children (5%) in the abla-

tion group and 12 of 27 (44%) in the control group had arrhythmic events. Three children in the control group had VF as the first presenting arrhythmia, and 1 of them died suddenly. The other 2 patients were successfully resuscitated and then ablated.

Current data are sufficient to consider revision of current guidelines and have led to several debates at many official cardiology congresses worldwide. In light of the recently published data prophylactic RF ablation can be safely and appropriately performed in asymptomatic high-risk patients. Low-risk patients may choose prophylactic ablation at the time of EPT when the catheters are in place, although it appears to be unjustified as complications may exceed the potential benefit. Nevertheless, we believe that at present our results in terms of benefits and risks may be extended to the general electrophysiology community. The results of a recent survey submitted worldwide to the EP community indicated that most electrophysiologists share our point of view, agreeing with risk stratification by EP testing and prophylactic ablation in high risk subjects.

### Survey Background

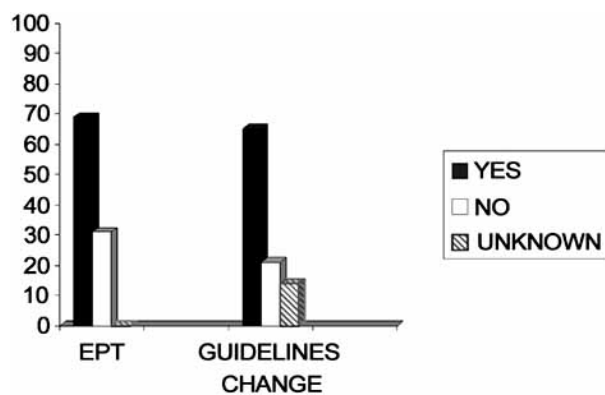
Although the Wolff-Parkinson-White syndrome is frequently associated with AVRT, there is a lifelong risk of sudden cardiac death due to atrial fibrillation, with rapid anterograde conduction over the accessory pathway to the ventricles, resulting in ventricular fibrillation. Reports among symptomatic patients with WPW syndrome have found that ventricular fibrillation occurred in 2.2% of patients over a 16-year period, while natural history data in asymptomatic patients reveal a sudden death rate of 1 per 1000 patient-years of follow-up. As a consequence, the possibility of cardiac arrest or sudden cardiac death must be always taken in consideration in each and every patient with an incidental WPW ECG pattern. Invasive electrophysiologic studies can determine arrhythmias inducibility, accessory pathway location and number, and tachyarrhythmia mechanism. In addition, invasive testing can determine conduction characteristics of accessory pathways to possibly stratify risk for potential sudden death. These include inducibility of AVRT and/or AF with shortest preexcited R-R interval of < 240 ms, multiple accessory pathways and a short effective refractory period for anterograde conduction across the accessory pathway. As catheter ablation techniques have improved, electrophysiology study (EPS) and radio frequency ablation (RFA) have become safe even in pediatric patients. A recent survey on asymptomatic WPW subjects published in 2003 demonstrated that at present most pediatric electrophysiologists in the States despite conservative Guidelines recommendations use routine ET testing to identify children at risk and RF ablation of accessory pathway in those considered at high risk [38]. We have hypothesized that at present in the era of RF ablation many subjects incidentally found with asymptomatic ventricular preexcitation are increasingly being referred for electrophysiologic evaluation in many electrophysiologic centers worldwide, with RFA when appropriate. Therefore, in this survey, we sought to investigate the magnitude of the problem and what approach the electrophysiologists are using in the asymptomatic WPW population. We also asked an opinion on the possibility of revisiting current guidelines in asymptomatic subjects with WPW ECG pattern.

### Survey Questionnaire

In March 2006, a 10-question survey was sent to 111 electrophysiologic centers worldwide. Centers were selected from the following sources: the Heart Rhythm Society member list, the ESC member list and official lists of working groups on arrhythmias in different countries of Europe; Asia; North America; and Oceania. The selected institutions were contacted by e-mail in all cases. For centers not responding after the first contact, no further contact was attempted. The 10 questions addressed the following issues: Do you think that sudden death in a previously asymptomatic subject is an

important issue that should be solved? Do you think all children or adolescents with WPW know exactly how to recognize symptoms of tachyarrhythmias? Do you reckon that a simple, no cost ECG performed in all newborns in the Neonatology department could be a useful tool for identifying WPW neonates? Are you currently performing a risk stratification for asymptomatic WPW subjects? If so, how many asymptomatic patients with WPW syndrome have undergone noninvasive or invasive risk stratification at your center? Are you currently performing prophylactic catheter ablation for high risk asymptomatic WPW? Do you think that in the day of RF and cryoablation we will never really have a defined natural history of WPW syndrome with which make decisions. How many asymptomatic adult patients (>18 years) with WPW syndrome have you seen at your center? How many asymptomatic children or adolescents ( $\leq 18$  years) with WPW have you seen? Do you believe that current guidelines should be revisited?

The deadline for final collection was the end of May 2006. All data were sent to an independent statistical center for analysis. The questionnaire was conceived to investigate clinical practices over a large number of centers around the world in the current strategy treatment among subjects with asymptomatic ventricular preexcitation and to evaluate potential changes in current guidelines for such population. A total of 100 replies were received from 111 practicing electrophysiologists. The results demonstrate that most electrophysiologists agree with EP testing for risk stratification and prophylactic ablation in high risk subjects (Fig. 1).



**Fig. (1).** The figure shows that in subjects with asymptomatic ventricular preexcitation about the 70% of electrophysiologists perform invasive electrophysiologic testing for risk stratification and prophylactic ablation and that more than 60 percent suggest to revisit the current guidelines.

## REFERENCES

- [1] Berkman NL, Lamb LE. The Wolff-Parkinson-White electrocardiogram: A follow-up study of five to twenty-eight years. *N Engl J Med* 1968; 278: 492-4.
- [2] Mantakas ME, McCue CM, Miller WW. Natural history of Wolff-Parkinson-White syndrome discovered in infancy. *Am J Cardiol* 1978; 41: 1097-103.
- [3] Giardina AC, Ehlers KH, Engle MA. Wolff-Parkinson-White in infants and children: a long-term follow-up study. *Br Heart J* 1972; 34: 839-46.
- [4] Smith RF. The Wolff-Parkinson-White syndrome as an aviation risk. *Circulation* 1964; 29: 672-9.
- [5] Gillette PC, Garson A Jr, Kugler JD. Wolff-Parkinson-White syndrome in children: Electrophysiologic and pharmacologic characteristics. *Circulation* 1979; 60: 1487-95.
- [6] Munger TM, Packer DL, Hammill SC, Trusty JM, Espinosa RE, Shen WK, *et al.* A population study of the natural history of Wolff-Parkinson-White syndrome in Olmsted county, Minnesota, 1953-1989. *Circulation* 1993; 87: 866-73.
- [7] Flensted-Jensen E. Wolff-Parkinson-White syndrome: A long-term follow-up of 47 cases. *Acta Med Scand* 1969; 186: 65-74.
- [8] Klein GJ, Bashore TM, Sellers TD, Pritchett EL, Smith WM, Gallagher JJ. Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *N Engl J Med* 1979; 301: 1080-5.
- [9] Montoya PT, Brugada P, Smeets J, Talajic M, Della Bella P, Lezaun R, *et al.* Ventricular fibrillation in the Wolff-Parkinson-White syndrome. *Eur Heart J* 1991; 12: 144-50.
- [10] Timmermans C, Smeets JL, Rodriguez LM, Vrouchos G, van den Dool A, Wellens HJ. Aborted sudden death in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1995; 76: 492-4.
- [11] Guize L, Soria R, Chaouat JC, Chretien JM, Houe D, Le Heuzey JY. Prevalence et evolution du syndrome de Wolff-Parkinson-White syndrome dans une population de 138 048 sujets. *Ann Med Interne (Paris)* 1985; 136 : 474-8
- [12] Sarubbi B, Scognamiglio G, Limongelli G, Mercurio B, Pacileo G, Pisacane C, *et al.* Asymptomatic ventricular pre-excitation in children and adolescents: a 15 year follow up study. *Heart* 2003; 89: 215-7.
- [13] Russel MW, Dorostkar PC, Dick M. Incidence of catastrophic events associated with the Wolff-Parkinson-White syndrome in young patients: diagnostic and therapeutic dilemma. *Circulation* 1993; 88(Suppl II): II-484 (abstract).
- [14] Deal BJ, Dick M, Beerman L. Cardiac arrest in young patients with the Wolff-Parkinson-White syndrome. *Pacing Clin Electrophysiol* 1995; 18(Suppl II): 815 (abstract).
- [15] Rodriguez LM, de Chillou C, Schlapfer J, Metzger J, Baiyan X, van den Dool A, *et al.* Age at onset and gender of patients suffering from different types of supraventricular tachycardias. *Am J Cardiol* 1992; 70: 1213-5.
- [16] Wellens HJ, Rodriguez LM, Timmermans C, Smeets JP. The asymptomatic patient with Wolff-Parkinson-White electrocardiogram. *Pacing Clin Electrophysiol* 1997; 20: 2082-6.
- [17] Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of electrocardiographic preexcitation in men. The Manitoba follow-up study. *Ann Intern Med* 1992; 116: 456-60.
- [18] Klein GJ, Yee R, Sharma AD. Longitudinal electrophysiologic assessment of asymptomatic patients with the Wolff-Parkinson-White electrocardiographic pattern. *N Engl J Med* 1989; 320: 1229-33.
- [19] Goudevenos JA, Katsouras CS, Graekas G, Argiri O, Giogiakas V, Sideris DA. Ventricular pre-excitation in the general population: a study on the mode of presentation and clinical course. *Heart* 2000; 83: 29-34.
- [20] Teo WS, Klein GJ, Guiraudon GM, Yee R, Leitch JW, McLellan D, *et al.* Multiple accessory pathways in the Wolff-Parkinson-White syndrome as a risk factor for ventricular fibrillation. *Am J Cardiol* 1991; 67: 889-91.
- [21] Bremilla-Perrot B, Ghawi R. Electrophysiological characteristics of asymptomatic Wolff-Parkinson-White syndrome. *Eur Heart J* 1993; 14: 511-5.
- [22] Milstein S, Sharma AD, Guiraudon GN, Klein GJ. An algorithm for the electrocardiographic localization of accessory pathways in the Wolff-Parkinson-White syndrome. *Pacing Clin Electrophysiol* 1987; 10: 555-63.
- [23] Fitzsimmons PJ, McWhirter PD, Peterson DW, Kruyer WB. The natural history of Wolff-Parkinson-White syndrome in 228 military aviators: A long-term follow-up of 22 years. *Am Heart J* 2001; 142: 530-6.
- [24] Satoh M, Aizawa Y, Funazaki T, Niwano S, Ebe K, Miyajima S, *et al.* Electrophysiologic evaluation of asymptomatic patients with the Wolff-Parkinson-White pattern. *Pacing Clin Electrophysiol* 1989; 12: 413-20.
- [25] Beckman KJ, Gallastegui JL, Bauman JL, Hariman RJ. The predictive value of electrophysiologic studies in untreated patients with Wolff-Parkinson-White syndrome. *J Am Coll Cardiol* 1990; 15: 640-7.
- [26] Leitch JW, Klein GJ, Yee R, Murdock C. Prognostic value of electrophysiology testing in asymptomatic patients with Wolff-Parkinson-White pattern. *Circulation* 1990; 82: 1718-23.
- [27] Fukatani M, Tanigawa M, Mori M, Konoe A, Kadana M, Shimizu A, *et al.* Prediction of a fatal atrial fibrillation in patients with asymptomatic Wolff-Parkinson-White pattern. *Jpn Circ J* 1990; 54: 1331-9.
- [28] Antz M, Weib C, Volkmer M, Hebe J, Ernst S, Ouyang F, *et al.* Risk of sudden death after successful accessory atrioventricular

- pathway ablation in resuscitated patients with Wolff-Parkinson-White syndrome. *J Cardiovasc Electrophysiol* 2002; 13: 231-6.
- [29] Basso C, Corrado D, Rossi L, Thiene G. Ventricular preexcitation in children and young adults: atrial myocarditis as a possible trigger of sudden death. *Circulation* 2001; 103: 269-75.
- [30] Weng KP, Wolff GS, Young ML. Multiple accessory pathways in pediatric patients with Wolff-Parkinson-White syndrome. *Am J Cardiol* 2003; 91: 1178-83.
- [31] Huang JL, Chen SA, Tai CT, Chiang CE, Lee SH, Chiou CW *et al.*, Long-term results of radiofrequency catheter ablation in patients with multiple accessory pathways. *Am J Cardiol* 1996; 78: 1375-79.
- [32] Zipes DP, DiMarco JP, Gillette PC, Jackman WM, Myerburg RJ, Rahimtoola SH, *et al.* Guidelines for clinical intracardiac electrophysiological and catheter ablation procedures. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Intracardiac Electrophysiologic and Catheter Ablation Procedures), developed in collaboration with the North American Society of Pacing and Electrophysiology. *J Am Coll Cardiol* 1995; 26: 555-73.
- [33] Blomstrom-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, *et al.* American College of Cardiology; American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines. Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias. *Circulation* 2003; 108: 1871-909.
- [34] Friedman RA, Walsh EP, Silka MJ, Calkins H, Stevenson WG, Rhodes LA, *et al.* NASPE Expert Consensus Conference: Radiofrequency catheter ablation in children with and without congenital heart diseases. Report of the Writing Committee. *Pacing Clin Electrophysiol* 2002; 25: 1000-17.
- [35] Inoue K, Igarashi H, Fukushima J, Ohno T, Joh K, Hara T. Long-term prospective study on the natural history of Wolff-Parkinson-White syndrome detected during a heart screening program at school. *Acta Paediatr* 2000; 89: 542-5.
- [36] Sharma AD, Yee R, Guiraudon G, Klein GJ. Sensitivity and specificity of invasive and non-invasive testing for risk of sudden death in Wolff-Parkinson-White syndrome. *J Am Coll Cardiol* 1987; 10: 373-81.
- [37] Triedman J, Perry J, Van Hare G, Pappone C, Santinelli V. Risk stratification for prophylactic ablation in asymptomatic Wolff-Parkinson-White syndrome. *New Engl J Med* 2005; 352: 92-3.
- [38] Campbell RM, Strieper MJ, Frias P, Collins KK, Van Hare GF, Dubin AM. Survey of current practice electrophysiologists for asymptomatic Wolff-Parkinson-White syndrome. *Pediatrics* 2003; 111: e245-7.
- [39] McDaniel GM, Van Hare GF. Catheter ablation in children and adolescents. *Heart Rhythm* 2006; 3: 95-101.
- [40] Pappone C, Santinelli V, Rosanio S, Vicedomini G, Nardi S, Pappone A, *et al.* Usefulness of invasive electrophysiologic testing to stratify the risk of arrhythmic events in asymptomatic patients with Wolff-Parkinson-White pattern: results from a large prospective long-term follow-up study. *J Am Coll Cardiol* 2003; 41: 239-44.
- [41] Pappone C, Santinelli V, Manguso F, Augello G, Santinelli O, Vicedomini G, *et al.* A randomized study of prophylactic ablation in asymptomatic patients with the Wolff-Parkinson-White syndrome. *N Engl J Med* 2003; 349: 1803-11.
- [42] Pappone C, Manguso F, Santinelli R, Vicedomini G, Sala S, Paglino G, *et al.* Radiofrequency ablation in children with asymptomatic Wolff-Parkinson-White syndrome. *N Engl J Med* 2004; 351: 1197-205.
- [43] Pappone C, Santinelli V. Catheter ablation should be performed in asymptomatic patients with Wolff-Parkinson-White. *Circulation* 2005; 112: 2209-17.
- [44] Pappone C, Santinelli V. Response to wellens. *Circulation* 2005; 112: 2218.
- [45] Kitada M, Uheda K, Nakagawa T, Yamaguchi Y. Follow-up study of the arrhythmic graduates from the schools under the Heart Disease Program for students in Osaka. *Jpn Circ J* 1984; 48: 1388-92.
- [46] Pietersen AH, Andersen ED, Sandoe E. Atrial fibrillation in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1992; 70: 38A-43A.
- [47] Dubin AM, Collins KK, Chiesa N, Hanisch D, Van Hare GF. The use of electrophysiologic testing to assess risk in children with Wolff-Parkinson-White syndrome. *Cardiol Young* 2002; 12: 248-52.
- [48] Bromberg BI, Lindsay BD, Cain ME, Cox JL. Impact of clinical history and electrophysiologic characterization of accessory pathways on management strategies to reduce sudden death among children with Wolff-Parkinson-White syndrome. *J Am Coll Cardiol* 1996; 27: 690-5.

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