

RAPID COMMUNICATION

P wave dispersion is prolonged in patients with Wilson's disease

Nurcan Arat, Sabite Kacar, Zehra Golbasi, Meral Akdogan, Yeliz Sokmen, Sedef Kuran, Ramazan Idilman

Nurcan Arat, Zehra Golbasi, Yeliz Sokmen, Türkiye Yüksek İhtisas Hospital, Clinic of Cardiology, Sıhhiye 06100, Ankara, Turkey

Sabite Kacar, Meral Akdoğan, Sedef Kuran, Türkiye Yüksek İhtisas Hospital, Clinic of Gastroenterology, Sıhhiye 06100, Ankara, Turkey

Ramazan Idilman, Ankara University Faculty of Medicine, Department of Gastroenterology, Cebeçi Campus 06590, Ankara, Turkey

Author contributions: Arat N, Kacar S, Golbasi Z designed research; Arat N, Kuran S, Akdogan M, Idilman R performed research; Arat N, Sokmen Y analyzed data; Arat N and Kacar S wrote the paper.

Correspondence to: Nurcan Arat, Türkiye Yüksek İhtisas Hospital, Clinic of Cardiology, Sıhhiye 06100, Ankara, Turkey. aratnurcan@gmail.com

Telephone: +90-505-502 5077 Fax: +90-312-362 4502

Received: October 1, 2007 Revised: December 11, 2007

Key words: Wilson's disease; Electrocardiography; P wave duration; P wave dispersion; Atrial depolarization

Peer reviewer: Valerio Nobili, Dr, Liver Unit, Research Institute, Bambino Gesù Children's Hospital, S. Onofrio 4 Square, Rome 00165, Italy

Arat N, Kacar S, Golbasi Z, Akdogan M, Sokmen Y, Kuran S, Idilman R. P wave dispersion is prolonged in patients with Wilson's disease. *World J Gastroenterol* 2008; 14(8): 1252-1256 Available from: URL: <http://www.wjgnet.com/1007-9327/14/1252.asp> DOI: <http://dx.doi.org/10.3748/wjg.14.1252>

Abstract

AIM: To investigate the P wave dispersion as a non-invasive marker of intra-atrial conduction disturbances in patients with Wilson's disease.

METHODS: We compared Wilson's disease patients ($n = 18$) with age matched healthy subjects ($n = 15$) as controls. The diagnosis was based on clinical symptoms, laboratory tests (ceruloplasmin, urinary and hepatic copper concentrations). P wave dispersion, a measurement of the heterogeneity of atrial depolarization, was measured as the difference between the duration of the longest and the shortest P-waves in 12 lead electrocardiography.

RESULTS: All the patients were asymptomatic on cardiological examination and have sinus rhythm in electrocardiography. Left ventricular and left atrial diameters, left ventricular ejection fraction and left ventricular mass index were similar in both groups. The Wilson's disease patients had a significantly higher P wave dispersion compared with the controls (44.7 ± 5.8 vs 25.7 ± 2.5 , $P < 0.01$).

CONCLUSION: There was an increase in P wave dispersion in cardiologically asymptomatic Wilson's disease patients which probably represents an early stage of cardiac involvement.

© 2008 WJG. All rights reserved.

INTRODUCTION

The persistence of P-wave duration is an accepted indicator of a disturbance in the interatrial conduction^[1,2]. P wave dispersion (PWD) constitutes an important contribution to the field of noninvasive electrocardiology and is defined as the difference between the longest and shortest P wave duration recorded from surface electrocardiogram (ECG) leads. PWD has been thoroughly examined in a number of diseases including hypertension, coronary artery disease, coronary artery bypass surgery, and paroxysmal atrial fibrillation (AF)^[3-7]. Therefore, it has been suggested that PWD can be used to diagnose patients with a high risk of AF^[8-13]. Wilson's disease is a severe genetic metabolic disorder, which is associated with intracellular copper overload and multiple organ involvement. Cardiac manifestations in Wilson's disease include arrhythmias, cardiomyopathy, cardiac death, and autonomic dysfunction^[14]. To our knowledge, no previous studies have compared P wave duration and PWD of Wilson's disease patients to healthy controls. The aim of this study was to investigate the PWD as a non-invasive marker of intra-atrial conduction disturbance in patients with Wilson's disease.

MATERIALS AND METHODS

Subjects

Eighteen cardiologically asymptomatic patients with Wilson's disease and 15 healthy subjects were included in the study. We excluded patients with previous acute myocardial infarction, thyroid dysfunction, uncontrolled diabetes mellitus, chronic renal disease, valvular heart disease, cardiomyopathy, chronic obstructive pulmonary disease, systemic

or pulmonary hypertension and alcohol abuse. All of the patients were in sinus rhythm and none were taking medications like antiarrhythmics, tricyclic antidepressants, antihistaminic and antipsychotics. The diagnosis of Wilson's disease was established based on the clinical manifestations, family history of neuropsychiatric manifestations, jaundice, and premature death attributable to Wilson's disease, evidence of Kayser-Fleischer rings on slit lamp examination, low serum copper and ceruloplasmin assay, and increased 24-h urinary excretion of copper. Radiologic investigations included a cranial computed tomography (CT) scan with or without iodinated contrast and/or magnetic resonance imaging (MRI) and X-rays of long bones, pelvis, and chest to evaluate for skeletal abnormalities^[15]. The diagnosis is confirmed by the liver biopsy and quantitative liver copper assay^[16].

Echocardiographic measurements

In all subjects, two-dimensional, M-mode pulsed and color flow Doppler echocardiographic examinations (Vivid 7 Dimension, GE, Horten, Norway) were performed by the same examiner. Internal left ventricular (LV) end-diastolic and end-systolic diameters and interventricular septal and posterior wall thickness at end-diastole, and left atrial dimension were measured from parasternal long axis window in M-mode echocardiography^[17]. The ejection fraction of the left ventricle was obtained using modified Simpson's method^[18].

Conventional Doppler echocardiography

Early diastolic wave peak velocity (E), late diastolic wave peak velocity (A), early to late velocities (E/A) ratio and E wave deceleration time of left ventricular inflow velocities were measured by pulse wave Doppler placing the sample volume in-between the tips of the mitral valve leaflets in apical four-chamber window. Isovolumic relaxation time (IVRT) was obtained from the apical-five-chamber view by placing the sample volume between the tip of the mitral anterior leaflet and left ventricle outflow tract.

Electrocardiography

Twelve-lead ECGs of all patients at rest, with 1 mV/cm amplitude and 50 mm/s rate, were obtained. The P-wave onset was defined as the first atrial deflection from the isoelectric line and the offset was the return of the atrial signal to baseline. Patients whose measurements could be performed in at least 8 derivations were included in the study. In all patients, derivations were excluded if the beginning or the ending of the P wave could not be clearly identified.

Maximum P wave duration (P_{max}) is defined as the longest and minimum P wave duration (P_{min}) is defined as the shortest P wave duration. PWD defined as difference between P_{max} and P_{min} . All the measurements were repeated three times and average values were calculated for each of electrocardiographic parameter. All of the measurements were performed using the same experienced investigators blind to the subject's clinical status. Intra-observer and inter-observer variability was assessed in a random sample of 15 ECG (10 from patients who have Wilson's disease

Table 1 The demographic and clinical characteristics of the study population

	Wilson's patients (n = 18)	Control group (n = 15)	P
Age (yr)	49 ± 26	44 ± 11	0.424
Left atrium (cm)	3.1 ± 0.4	3.2 ± 0.6	0.240
Left ventricular end diastolic diameter (cm)	4.5 ± 0.3	4.7 ± 0.4	0.316
Left ventricular end systolic diameter (cm)	2.8 ± 0.3	3.0 ± 0.3	0.320
Interventricular septum thickness (cm)	0.8 ± 0.1	0.9 ± 0.1	0.435
Posterior wall thickness (cm)	0.9 ± 0.1	0.8 ± 0.1	0.349
Ejection fraction (%)	66.6 ± 6.6	64.6 ± 6.1	0.335
E (cm/s)	93.7 ± 14.3	88.2 ± 12.5	0.323
A (cm/s)	68.8 ± 14.6	75.2 ± 25.1	0.303
E/A	1.3 ± 0.4	0.8 ± 0.2	0.090
EDT (ms)	177 ± 53.2	167 ± 34.2	0.213
IVRT (ms)	68.4 ± 12.0	72.2 ± 22.4	0.275
P wave dispersion (ms)	44.7 ± 5.8	25.7 ± 2.5	0.007
Minimum P wave duration (ms)	65 ± 12	74 ± 10	0.239
Maximum P wave duration (ms)	109 ± 8	102 ± 10	0.031

and 5 from control subjects) by a second investigator. The study was approved by the local ethics committee of our institution, and all patients gave written informed consent.

Statistical analysis

The SPSS statistical software package (11.0) was used to perform all statistical calculations. Number of sample is expressed as *n*, continuous variables were expressed as mean ± SD, and categorical variables as percentages. Pearson correlations were used to compare the association between indexes. Categorical variables were compared by Pearson Chi-square test. Comparisons of continuous variables between two groups have been performed by means of unpaired Student's *t* test. For all tests, *P* < 0.05 was considered statistically significant.

RESULTS

The study included 18 patients (age: 49 ± 26 years, range 10-49 years) with Wilson's disease and 15 healthy controls (age: 44 ± 11 years, range 25-50 years). In Wilson's disease patients, the patients' age at the diagnosis was 42 ± 18 years (range, 2.5-42 years), the mean disease duration was 9.6 ± 7 years (range, 1-29 years). Serum copper, ceruloplasmin and urinary copper excretion were 1670 ± 800 µg/L, 300 ± 120 mg/L, 167 ± 80 µg/dL, respectively. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin, total cholesterol, low density lipoprotein, high density lipoprotein, and triglyceride levels were 53.2 ± 42 IU/L, 45.6 ± 35 IU/L, 138 ± 18 mg/L, 131 ± 37 mg/dL, 50 ± 31 mg/dL, 66 ± 23 mg/dL, and 95 ± 16 mg/dL respectively.

The demographic and clinical characteristics of the Wilson's patients and the controls were shown in Table 1. There was no significant difference between the two groups in regard to gender, age, body mass index (BMI), heart rate or blood pressure. All Wilson's patients were treated with copper chelation therapy. Seventeen of the

Wilson's patients have been treated with D -penicillamine (0.75-1 g p.o., t.i.d.) and one patient was switched to trientine (750 mg, p.o. t.i.d.) of because drug related thrombocytopenia.

P_{max} and PWD were significantly higher in Wilson's patients than controls. However, there was no significant difference in P_{min} between the two groups (Table 1; A = Transmitral late diastolic peak velocity, E = Transmitral early diastolic peak velocity, EDT = E wave deceleration time, IVRT = Isovolumic relaxation time).

PWD was considerably correlated only with the age at diagnosis ($r = -0.606$, $P = 0.048$), serum copper level ($r = -0.801$, $P = 0.009$) and mitral E wave velocity ($r = -0.724$, $P = 0.027$) in patients with Wilson's disease. We were not able to find any statistically significant correlation between PWD and other clinical and echocardiographic parameters.

The intra-observer standard deviation for P_{max} , P_{min} and PWD were 10.3, 6.5, and 11 ms, respectively, and the corresponding intra-observer variability was 0.05%, 0.06%, and 0.2%, respectively. The inter-observer standard deviation for P_{max} , P_{min} and PWD were 10.5, 11.0, and 13.9 ms, respectively, and the corresponding inter-observer variability was 0.04%, 0.2%, and 0.5%, respectively. The percentage difference in P_{max} , P_{min} and PWD were 2.4%, 3.5%, and 6% within observers and 3%, 5.2%, and 5.9% between observers.

DISCUSSION

Wilson's disease is a severe genetic multisystem disorder associated with intracellular copper storage. Wilson's disease is characterized by an inadequate excretion of absorbed dietary copper *via* bile resulting in the accumulation of toxic amounts of copper in the liver and other organs. It is inherited as a rare autosomal recessive condition with an incidence of one in 40 000 live births in most populations, and with a calculated carrier frequency in the general population of one in 90^[19,20]. Copper is an essential micronutrient but ionic copper is toxic. The toxic effects are thought to be mediated by the generation of reactive oxygen free radical species in Wilson's patients^[19]. Cardiac involvement in Wilson's disease has rarely been recognized. Cardiac manifestations in Wilson's disease include arrhythmias, cardiomyopathy, cardiac death, and autonomic dysfunction^[14,19]. Electrocardiographic abnormalities occurred in 34 percent, including left ventricular hypertrophy, biventricular hypertrophy, early re-polarization, ST depression and T inversion, premature atrial or ventricular contractions, atrial fibrillation, sino-atrial block and Mobitz type 1 atrio-ventricular block. Asymptomatic orthostatic hypotension, an abnormal response to the Valsalva maneuver, ventricular fibrillation, and dilated cardiomyopathy can be occurred in Wilson's disease^[14].

The major pathological findings of the myocardium in Wilson's disease included the presence of interstitial and replacement myocardial fibrosis, intra-myocardial small vessel disease, focal myocarditis and cardiac hypertrophy, AV nodal degeneration and occlusive atherosclerosis in early ages^[21]. These alterations are non-specific, but they are similar to those observed in other cardiomyopathies^[21,22]. Their existence in a relatively young group of

patients without other significant etiology for the development of heart disease, suggests the possibility of a direct relationship between Wilson's disease and cardiac degeneration^[20].

Therefore, we investigated PWD in patients with Wilson's disease patients. PWD is a new electrocardiographic marker that has been associated with the heterogeneous and discontinuous propagation of sinus impulses. Furthermore, the correlation between the presence of intra-atrial conduction abnormalities and the induction of paroxysmal AF has been well documented^[8-10,23,24]. Prolonged P wave duration and increased PWD have been reported to carry an increased risk for atrial fibrillation^[5-7,17]. Therefore, it has been suggested that PWD can be used to diagnose patients with a high risk for developing AF^[8-10]. To our knowledge, this is the first study that has investigated the P wave duration and PWD changes in Wilson's disease patients. This study shows that P_{max} and PWD are higher in Wilson's disease patients than control subjects. These results suggest that Wilson's disease patients may be under the risk for atrial fibrillation. This study also shows that PWD was correlated with mitral E wave velocity which is a parameter of left ventricular diastolic function and the serum copper level. Previously, it has been reported that PWD was associated with diastolic dysfunction and coronary artery disease^[3,25,26].

The precise mechanism of arrhythmias seen in Wilson's disease patients is not clear. A recent report Kaduk *et al*^[27] describing cardiomyopathy in Wilson's disease, suggested that mitochondrial alterations were the consequence of the accumulation of myocardial copper. These alterations are non-specific, and in some cases of limited severity; however, in previous study it was concluded that cardiac degeneration might have contributed to the death of Wilson's patients^[27]. PWD may well be associated with autonomic dysfunction in patients with Wilson's disease^[27]. Dysautonomia, often subclinical, is only one of the many features of Wilson's disease^[28]. A central, rather than peripheral mechanism is hypothesized. Sympathetic and parasympathetic arms are affected equally. The abnormality is independent of involvement of the liver and the duration and severity of Wilson's disease^[29].

Previous experiments showed that electrical remodeling of atrial myocardium could be induced by autonomic nervous transmitters and suggested that autonomic nerve activity was an important factor to promote AF episodes^[30]. This study population is relatively small and therefore our results should not be extrapolated to all Wilson's patients. Further studies are necessary to investigate the frequency of atrial arrhythmias by rhythm holter in patients with Wilson's disease, who have or do not have high PWD.

Furthermore, one of the relative limitations of our study was that we could not use the method of digital recording and storing of 12-lead electrocardiograms with onscreen measurement of P waves duration which provides the most accurate method for PWD calculation^[31]. Secondly, the ability of P wave duration and PWD to predict future atrial fibrillation episodes was not checked in present study, since the patients included in this work were not followed-up. But, it has been well documented previously that prolonged P wave duration and increased PWD carry

an increased risk for atrial fibrillation^[8-10,23,24] and therefore, it has been suggested that PWD can be used to diagnose patients with a high risk for developing AF^[8-10].

Consequently, involvement of the heart may be seen in patients with Wilson's disease even in the absence of clinical cardiac manifestations. In this study, P_{max} and PWD were found to be higher in patients with Wilson's disease than healthy control subjects. Therefore, the patients with Wilson's disease who have increased PWD should be closely followed for atrial arrhythmias.

COMMENTS

Background

Wilson's disease is a rare severe genetic metabolic disorder associated with intracellular copper overload and related complications. Cardiac manifestations in Wilson's disease include arrhythmias, cardiomyopathy, cardiac death, and autonomic dysfunction. P wave dispersion, a measurement of the heterogeneity of atrial depolarization.

Research frontiers

No previous studies have compared P wave duration and P wave dispersion (PWD) of Wilson's disease patients to healthy controls. The aim of this study was to investigate the PWD as a non-invasive marker of intra-atrial conduction disturbance in patients with Wilson's disease.

Innovations and breakthroughs

Prolonged P wave duration and increased PWD have been reported to carry an increased risk for atrial fibrillation. Therefore, it has been suggested that PWD can be used to diagnose patients with a high risk for developing AF. In previous reports researchers showed that electrical remodeling of atrial myocardium could be induced by autonomic nervous transmitters and suggested that autonomic nerve activity was an important factor to promote AF episodes. This study also shows that PWD was correlated with mitral E wave velocity which is a parameter of left ventricular diastolic function and the serum copper level. Previously, it has been reported that PWD was associated with diastolic dysfunction and coronary artery disease.

Applications

Prolonged P wave duration and increased PWD carry an increased risk for AF. Therefore, it has been suggested that PWD can be used to diagnose patients with a high risk for developing AF. This study shows that P_{max} and PWD are higher in Wilson's disease patients than control subjects. These results suggest that Wilson's disease patients may be under the risk for atrial fibrillation.

Terminology

Wilson's disease is a severe genetic metabolic disorder associated with intracellular copper overload and multiple organ involvement. P wave dispersion was measured as the difference between the duration of the longest and the shortest P-waves in 12 lead electrocardiography.

Peer review

This report is original and has to be considered interesting. The authors aimed to investigate the P wave dispersion as a non-invasive marker of intra-atrial conduction disturbances in patients with Wilson's disease. This rather small but homogenous patient population showed promising results with the application of PWD at such a rare genetic disorder.

REFERENCES

- 1 Bayes De Luna A. Electrocardiographic alteration due to atrial pathology. In: Clinical electrocardiography: a textbook. New York: Futura Company, 1998: 169-171
- 2 Willems JL, Robles de Medina EO, Bernard R, Coumel P, Fisch C, Krikler D, Mazur NA, Meijler FL, Mogensen L, Moret P. Criteria for intraventricular conduction disturbances and pre-excitation. World Health Organization/International Society and Federation for Cardiology Task Force Ad Hoc. *J Am Coll Cardiol* 1985; **5**: 1261-1275
- 3 Yilmaz R, Demirbag R. P-wave dispersion in patients with stable coronary artery disease and its relationship with severity of the disease. *J Electrocardiol* 2005; **38**: 279-284
- 4 Dogan A, Ozaydin M, Nazli C, Altinbas A, Gedikli O, Kinay O, Ergene O. Does impaired left ventricular relaxation affect P wave dispersion in patients with hypertension? *Ann Noninvasive Electrocardiol* 2003; **8**: 189-193
- 5 Chandy J, Nakai T, Lee RJ, Bellows WH, Dzankic S, Leung JM. Increases in P-wave dispersion predict postoperative atrial fibrillation after coronary artery bypass graft surgery. *Anesth Analg* 2004; **98**: 303-310, table of contents
- 6 Perzanowski C, Ho AT, Jacobson AK. Increased P-wave dispersion predicts recurrent atrial fibrillation after cardioversion. *J Electrocardiol* 2005; **38**: 43-46
- 7 Senen K, Turhan H, Riza Erbay A, Basar N, Saatci Yasar A, Sahin O, Yetkin E. P-wave duration and P-wave dispersion in patients with dilated cardiomyopathy. *Eur J Heart Fail* 2004; **6**: 567-569
- 8 Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, Gialafos JE, Toutouzas PK. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. *Am Heart J* 1998; **135**: 733-738
- 9 Dilaveris PE, Gialafos EJ, Andrikopoulos GK, Richter DJ, Papanikolaou V, Poralis K, Gialafos JE. Clinical and electrocardiographic predictors of recurrent atrial fibrillation. *Pacing Clin Electrophysiol* 2000; **23**: 352-358
- 10 Dilaveris PE, Gialafos JE. P wave dispersion: a novel predictor of paroxysmal atrial fibrillation. *Ann Noninvasive Electrocardiol* 2001; **6**: 159-165
- 11 Gottdiener JS, Kitzman DW, Aurigemma GP, Arnold AM, Manolio TA. Left atrial volume, geometry, and function in systolic and diastolic heart failure of persons > or =65 years of age (the cardiovascular health study). *Am J Cardiol* 2006; **97**: 83-89
- 12 Tsang TS, Gersh BJ, Appleton CP, Tajik AJ, Barnes ME, Bailey KR, Oh JK, Leibson C, Montgomery SC, Seward JB. Left ventricular diastolic dysfunction as a predictor of the first diagnosed nonvalvular atrial fibrillation in 840 elderly men and women. *J Am Coll Cardiol* 2002; **40**: 1636-1644
- 13 Poli S, Barbaro V, Bartolini P, Calcagnini G, Censi F. Prediction of atrial fibrillation from surface ECG: review of methods and algorithms. *Ann Ist Super Sanita* 2003; **39**: 195-203
- 14 Kuan P. Cardiac Wilson's disease. *Chest* 1987; **91**: 579-583
- 15 Taly AB, Meenakshi-Sundaram S, Sinha S, Swamy HS, Arunodaya GR. Wilson disease: description of 282 patients evaluated over 3 decades. *Medicine* (Baltimore) 2007; **86**: 112-121
- 16 Brewer GJ, Yuzbasiyan-Gurkan V. Wilson disease. *Medicine* (Baltimore) 1992; **71**: 139-164
- 17 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; **58**: 1072-1083
- 18 Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; **2**: 358-367
- 19 Gaffney D, Fell GS, O'Reilly DS. ACP Best Practice No 163. Wilson's disease: acute and presymptomatic laboratory diagnosis and monitoring. *J Clin Pathol* 2000; **53**: 807-812
- 20 Frydman M. Genetic aspects of Wilson's disease. *J Gastroenterol Hepatol* 1990; **5**: 483-490
- 21 Factor SM, Cho S, Sternlieb I, Scheinberg IH, Goldfischer S. The cardiomyopathy of Wilson's disease. Myocardial alterations in nine cases. *Virchows Arch A Pathol Anat Histol* 1982; **397**: 301-311
- 22 Roberts WC, Ferrans VJ. Pathologic anatomy of the

- cardiomyopathies. Idiopathic dilated and hypertrophic types, infiltrative types, and endomyocardial disease with and without eosinophilia. *Hum Pathol* 1975; **6**: 287-342
- 23 **Leier CV**, Meacham JA, Schaal SF. Prolonged atrial conduction. A major predisposing factor for the development of atrial flutter. *Circulation* 1978; **57**: 213-216
- 24 **Aytemir K**, Ozer N, Atalar E, Sade E, Aksoyek S, Ovunc K, Oto A, Ozmen F, Kes S. P wave dispersion on 12-lead electrocardiography in patients with paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 2000; **23**: 1109-1112
- 25 **Gunduz H**, Binak E, Arinc H, Akdemir R, Ozhan H, Tamer A, Uyan C. The relationship between P wave dispersion and diastolic dysfunction. *Tex Heart Inst J* 2005; **32**: 163-167
- 26 **Yilmaz R**, Kasap H, Baykan M, Durmus I, Kaplan S, Celik S, Erdol C. Assessment of left ventricular function by Doppler tissue imaging in patients with atrial fibrillation following acute myocardial infarction. *Int J Cardiol* 2005; **102**: 79-85
- 27 **Kaduk B**, Metze K, Schmidt PF, Brandt G. Secondary athrocytotic cardiomyopathy--heart damage due to Wilson's disease. *Virchows Arch A Pathol Anat Histol* 1980; **387**: 67-80
- 28 **Cheema AN**, Ahmed MW, Kadish AH, Goldberger JJ. Effects of autonomic stimulation and blockade on signal-averaged P wave duration. *J Am Coll Cardiol* 1995; **26**: 497-502
- 29 **Meenakshi-Sundaram S**, Taly AB, Kamath V, Arunodaya GR, Rao S, Swamy HS. Autonomic dysfunction in Wilson's disease --a clinical and electrophysiological study. *Clin Auton Res* 2002; **12**: 185-189
- 30 **Li G**, Liu T, Liu E. Cardiac electrical stunning is a common feature of cardiac arrhythmias. *Med Hypotheses* 2006; **67**: 865-867
- 31 **Dilaveris P**, Batchvarov V, Gialafos J, Malik M. Comparison of different methods for manual P wave duration measurement in 12-lead electrocardiograms. *Pacing Clin Electrophysiol* 1999; **22**: 1532-1538

S- Editor Zhu WL L- Editor Li M E- Editor Liu Y