P-Wave Dispersion in Familial Dysautonomia

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ABSTRACT: **Background:** Familial dysautonomia is a hereditary disease characterized by dysfunction of the sensory and autonomic nervous systems. Studies in patients with familial dysautonomia have shown that abnormal cardiac autonomic denervation might influence repolarization. Autonomic tone also affects atrial conduction parameters and P-wave dispersion, which are predictive of atrial fibrillation.

Objectives: To examine the possible association of familial dysautonomia with abnormal atrial conduction and P-wave dispersion.

Methods: The study population included 12 patients with familial dysautonomia and age and gender-matched control subjects. All participants underwent a 12-lead electrocardiogram under strict conditions. P-wave lengths and P-wave dispersion were computed from a randomly selected beat and an averaged beat using designated computer software.

Results: There were no statistically significant differences between the groups in minimal, maximal and average P-wave duration or P-wave dispersion for a randomly selected beat. P-wave dispersion for an averaged beat was also similar. During 6 months follow-up, no supraventricular arrhythmias were documented in either group.

Conclusions: We found that patients with familial dysautonomia had P-wave dispersion parameters not significantly different from those of controls. Further research is required to clarify the effects of dysautonomia on atrial conduction in familial dysautonomia.

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KEY WORDS: arrhythmia, atrial fibrillation, cardiac autonomic denervation, familial dysautonomia, P wave

Familial dysautonomia is a rare genetic disease generally affecting Ashkenazi Jews [1]. It is characterized by abnormal development and abnormal function of the sensory and autonomic nervous system [1] as well as by progressive neural degeneration [2]. Clinical signs may be evident at a young age and include hypotonia, eating difficulties, dysregulation of body temperature and skin color, and, in some cases, dysautonomic crisis [3]. Cardiovascular autonomic denervation and dysregulation are common, and blood pressure may fluctuate considerably [1,4].

P-wave dispersion is defined as the difference between the longest and shortest P-wave duration recorded from multiple surface electrocardiographic leads [5]. An increase in P-wave duration and P-wave dispersion is apparently associated with heterogeneity in atrial conduction, posing a risk of occurrence and recurrence of atrial fibrillation [5,6]. P-wave dispersion was found to be a specific and sensitive marker in various clinical settings [5]. Moreover, there is evidence that atrial activation is subject to diurnal variations and that both atrial activation and P-wave dispersion may be influenced by the autonomic nervous system [5]. A study of healthy subjects noted an effect of the Valsalva maneuver on P-wave duration [7].

In a recent study of patients with familial dysautonomia, our group reported that cardiac anatomic abnormalities, namely cardiac remodeling and ventricular hypertrophy, were not unusual and were probably attributable to paroxysmal hypertension and autonomic dysfunction [1]. Furthermore, we noted abnormal repolarization parameters, possibly induced by the autonomic denervation [8]. Encouraged by these findings, we sought to evaluate atrial ECG parameters in patients with familial dysautonomia and to quantify the possible consequences of the autonomic dysfunction on atrial conduction.

PATIENTS AND METHODS

A comparative case series design was used. The research protocol was approved by the hospital's Institutional Review Board. All participants gave written informed consent.

The study group consisted of 12 patients with familial dysautonomia. Diagnosis was based on the presence of cardinal clinical features [9] and positive genetic testing. None of the patients had an additional acute or chronic clinical condition, nor were drugs taken to influence the electrocardiogram or heart rate. Twelve healthy subjects matched for gender and age served as controls.

PROCEDURE

Participants were asked to avoid smoking or intake of caffeinated beverages or other stimulants for 3 hours prior to the study and to avoid strenuous exercise for 24 hours prior to the study. The test was conducted between 4 and 6 p.m. to avoid circadian influences on ECG parameters. Room temperature was maintained at 20–23°C. Participants were asked to lie motionless for 10 minutes.

Electrodes were placed in anatomic positions according to routine procedure. ECG strips were recorded with a standard device for 10 seconds with the patient in a resting supine position. Inadequate quality readings were repeated. P-wave length was measured from all leads with custom-made computer software validated for accuracy and consistency. Subsequently, results were manually reevaluated by an investigator blinded to the clinical data and the automated results. In cases of disagreement between automated and manual measurements, the ECGs were reevaluated by another investigator, and the results of the two manual measurements were averaged. The maximal, minimal and average P-wave lengths were computed from one randomly selected beat in a steady state. P-wave dispersion was then calculated by subtracting the minimal P-wave length from the maximal P-wave length from 12 leads. In addition, 7–12 beats were averaged during the 10 seconds of ECG measurements. P-wave dispersion was computed for an averaged beat in a similar manner. Patients were followed for 6 months.

STATISTICAL ANALYSIS

Data were analyzed with Microsoft Excel version 2003 (Microsoft Corp., Seattle, WA, USA) and JMP version 7.0 (SAS Institute, Cary, NC). The results are presented as mean and standard deviations. Abnormal results were defined as more than 2 standard deviations from the normal range. Student *t*-test was used to compare results between the groups. A *P* value < 0.05 was considered statistically significant.

RESULTS

The mean age of the study group was 24.1 ± 11.4 years, and of the control group 23.5 ± 9.3 years ($P = 0.9$). The calculated P-wave length and P-wave dispersion parameters for the two groups are shown in Table 1. There was no statistically significant difference between groups in maximal, minimal and average P-wave length for a randomly selected beat. In addition, P-wave dispersion was similar in the two groups, both for a randomly selected beat (24.7 ± 7.6 ms in the study group, 22.5 ± 8 ms in the control group, $P = 0.5$) and for an averaged beat (26.3 ± 11.9 ms and 24.3 ± 8.1 ms, respectively, $P = 0.6$). The maximal P-wave length in the control group was similar to values reported in previous studies [10,11]. During 6 months of follow-up, no case of atrial fibrillation or other supraventricular arrhythmia was documented in either group.

Table 1. P-wave length and P-wave dispersion in patients with familial dysautonomia compared to control subjects

	Familial dysautonomia (N=12)	Control (N=12)	*P* value
Age (yrs)	24.1 ± 11.4	23.5 ± 9.3	NS
Maximal P (ms)	100.5 ± 11.1	107.3 ± 10.2	NS
Minimal P (ms)	75.8 ± 10.0	84.8 ± 11.4	NS
Average P (ms)	90.4 ± 10.8	97.6 ± 8.9	NS
P dispersion (ms)	24.7 ± 7.6	22.5 ± 8.0	NS
Averaged P dispersion (ms)	26.3 ± 11.9	24.3 ± 8.1	NS

NS = not significant (P › 0.05)

DISCUSSION

Atrial conduction is highly influenced by the autonomic nervous system. In a study of healthy subjects, isoproterenol and atropine were found to significantly shorten P-wave duration whereas epinephrine and beta-adrenegic receptor blocking agents significantly prolonged it [12].

An earlier study reported that the Valsalva maneuver can normalize high P-wave dispersion in patients with paroxysmal atrial fibrillation [7]. Interestingly, in normal subjects, the Valsalva maneuver caused an increase in P-wave duration and P-wave dispersion [7].

In patients with familial dysautonomia, the autonomic dysfunction is attributable to involvement of the intermediolateral spinal column and sympathetic ganglia. While the sympathetic system is usually highly affected [13], the parasympathetic abnormalities are usually less severe [2]. Patients with familial dysautonomia lack a normal heart rate response to autonomic stimuli, such as deep breathing [2]. Evaluation of the papillary light reflex in patients with familial dysautonomia yielded both sympathetic and parasympathetic abnormalities [13]. Moreover, heart rate variability studies in familial dysautonomia found that some patients have abnormal parasympathetic and sympathetic cardiac tone [14]. On functional imaging, post-ganglionic cardiac sympathetic fibers were also diminished [15]. Nevertheless, the present study showed that patients with familial dysautonomia do not have statistically significant prolonged P-wave length or P-wave dispersion compared with normal controls, despite the evident dysautonomia.

The mean P-wave dispersion calculated from a randomly selected beat in patients with familial dysautonomia and in controls was lower than 40 msec, which is considered normal [5,16]. This might indicate a lack of tendency towards abnormal atrial conduction in familial dysautonomia. The mean value of P-wave dispersion calculated from an averaged beat in familial dysautonomia patients was also lower than

40 msec. The lack of statistically significant higher P-wave dispersion in familial dysautonomia compared with controls and a mean value of averaged P-wave dispersion lower than 40 msec are supported by the lack of classical risk factors for atrial fibrillation or documentation of a higher prevalence of atrial fibrillation in patients with familial dysautonomia. Furthermore, during follow-up in the present study, no supraventricular arrhythmia was noted in either the study or control group.

STUDY LIMITATIONS

Our study group was relatively small because of the low prevalence of familial dysautonomia. Axelrod [15] verified great variability in clinical expression of familial dysautonomia. We are thus unable to establish if the results would have been different had we selected patients with a unique phenotype or patients with more severe abnormalities in autonomic nervous system function.

Although P-wave dispersion has proven to be a sensitive and specific predictor of supraventricular arrhythmias, there is no single standardized method for its calculation [5], which limits the comparison between different studies.

CONCLUSIONS

The present study is the first to evaluate atrial conduction parameters and P-wave dispersion in patients with familial dysautonomia. We found that P-wave length and P-wave dispersion in familial dysautonomia patients were similar to those of healthy controls. Further larger-scale, long-term studies with extended follow-ups are needed to clarify the effects of autonomic maneuvers on atrial conduction parameters in familial dysautonomia. The prolonged P-wave averaging technique and echocardiographic assessment of the atrium might be of value in future investigations.

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References

1. Nussinovitch U, Katz U, Nussinovitch M, Blieden L, Nussinovitch N. Echocardiographic abnormalities in familial dysautonomia. *Pediatr Cardiol* 2009; 30(8): 1068-74.
2. Nussinovitch U, Katz U, Nussinovitch M, Nussinovitch N. Deep breath test for evaluation of autonomic nervous system dysfunction in familial dysautonomia. *IMAJ Isr Med Assoc J* 2009; 11(10): 615-18.
3. Nussinovitch U, Katz U, Nussinovitch M, Nussinovitch N. Late ventricular potentials and QT dispersion in familial dysautonomia. *Pediatr Cardiol* 2009; 30(6): 747-51.
4. Nussinovitch N, Nussinovitch M, Peleg E, Rosenthal T. 24-hour ambulatory blood pressure monitoring in children with familial dysautonomia. *Pediatr Nephrol* 2005; 20(4): 507-11.
5. Michelucci A, Bagliani G, Colella A, et al. P wave assessment: state of the art update. *Card Electrophysiol Rev* 2002; 6(3): 215-20.
6. Perzanowski C, Ho AT, Jacobson AK. Increased P-wave dispersion predicts recurrent atrial fibrillation after cardioversion. *J Electrocardiol* 2005; 38(1): 43-6.
7. Tukek T, Akkaya V, Demirel S, et al. Effect of Valsalva maneuver on surface electrocardiographic P-wave dispersion in paroxysmal atrial fibrillation. *Am J Cardiol* 2000; 85(7): 896-9, A10.
8. Nussinovitch U, Katz U, Nussinovitch M, Nussinovitch N. Beat-to-beat QT interval dynamics and variability in familial dysautonomia. *Pediatr Cardiol* 2010; 31(1): 80-4.
9. Axelrod FB. Hereditary sensory and autonomic neuropathies. Familial dysautonomia and other HSANs. *Clin Auton Res* 2002; 12 (Suppl 1): I2-14.
10. Kocer A, Karakaya O, Kargin R, Barutcu I, Esen AM. P wave duration and dispersion in multiple sclerosis. *Clin Auton Res* 2005; 15(6): 382-6.
11. Senen K, Turhan H, Riza Erbay A, et al. P-wave duration and P-wave dispersion in patients with dilated cardiomyopathy. *Eur J Heart Fail* 2004; 6(5): 567-9.
12. 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(2): 497-502.
13. Hilz MJ. Assessment and evaluation of hereditary sensory and autonomic neuropathies with autonomic and neurophysiological examinations. *Clin Auton Res* 2002; 12 (Suppl 1): I33-43.
14. Axelrod FB, Putman D, Berlin D, Rutkowski M. Electrocardiographic measures and heart rate variability in patients with familial dysautonomia. *Cardiology* 1997; 88(2): 133-40.
15. Axelrod FB. A world without pain or tears. *Clin Auton Res* 2006; 16(2): 90-7.
16. Dilaveris PE. P wave dispersion: does it have any clinical role? *Card Electrophysiol Rev* 1999; 3(4): 261–3.