

P-Wave Dispersion in Panic Disorder

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Background: P-wave dispersion (PWD) is defined as the difference between the maximum and the minimum P-wave (P_{max} and P_{min}, respectively) duration. Significant variation in cardiac atrial PWD has been correlated with changes in systemic autonomic tone such as during periods of anxiety. It is also known that the degree of PWD seen on 12-lead electrocardiogram (ECG) may be a predictor of susceptibility of the atrial myocardium to future atrial fibrillation (AF). Therefore, we firstly aimed to show an association between PWD and panic disorder, a state of high sympathetic tone. **Methods:** PWD was measured in 40 outpatients with panic disorder and in 40 physically and mentally healthy age- and gender-matched controls. In addition, the Panic Agoraphobia Scale (PAS) and the Hamilton Depression Rating Scale (HDRS) were scored concomitantly. **Results:** Both P_{max} and P_{min} were significantly higher than those of healthy controls. PWD was significantly greater in the panic disorder group than in the controls. As expected, the mean score on PAS was significantly higher for the panic disorder group than for the controls and correlated significantly with PWD. Heart rate (measured as RR intervals in milliseconds on electrocardiogram) did not differ significantly between the groups. **Conclusions:** The findings of the present study suggest that the disorder may be associated with an increase in PWD. This association may result from prolonged anxiety and increase in sympathetic modulation, which are main characteristics of panic disorder. **Key words:** P-wave dispersion, panic disorder, anxiety.

PWD = P-wave dispersion; **P_{max}** = maximum P-wave duration; **P_{min}** = minimum P-wave duration; **HRV** = heart rate variability; **AF** = atrial fibrillation; **ECG** = electrocardiogram; **PAS** = The Panic Agoraphobia Scale; **HDRS** = Hamilton Depression Rating Scale; **ANS** = autonomic nervous system; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders IV.

INTRODUCTION

Panic disorder is a severe syndrome associated with significant impairment to a patient's quality of life as well as his or her social life function. Comorbidity with depressive and addictive disorders is frequent, and it is considered by numerous authors as a risk factor for suicide. Symptoms of panic-like anxiety and panic disorder have been shown to be disproportionately prevalent among coronary artery disease patients, where panic disorder alone has been shown to affect approximately 10% to 50% of patients with established coronary artery disease (1). There is also evidence to suggest that panic disorder and panic-like anxiety is related to poorer coronary artery disease prognosis, including increased risk for post-myocardial infarction in-hospital complications (e.g., acute ischemia, re-infarction, sustained ventricular tachycardia, and ventricular fibrillation) and mortality (2).

In all anxiety disorders, symptoms are present that suggest the involvement of the autonomic nervous system (ANS). In panic attacks, which can occur in several anxiety disorders, ANS symptoms, such as palpitations, chest pain, and shortness of breath, are prevalent. In panic disorder, which is characterized by spontaneous panic attacks (3), several studies have investigated the involvement of the ANS (4). Recent studies have used the analysis of heart rate variability (HRV) as a tool to study the functioning of the ANS. This analysis of a simple,

noninvasive electrocardiogram (ECG) elucidates the influence of the ANS on short-term regulation of the cardiovascular system (5). HRV is primarily controlled by the continuous interplay of the sympathetic and parasympathetic (vagal) branches of the ANS (6). P-wave dispersion (PWD) has been defined as the difference between maximum and minimum P-wave duration (7). It is related to inhomogeneous and discontinuous propagation of sinus impulses through the atrial wall (7,8). Prolonged P-wave duration and increased PWD have been reported to be related to increased risk for atrial fibrillation (AF) (7–9).

To the best of our knowledge, PWD has not been analyzed in patients with panic disorder. The aim of the present study was to compare PWD in physically healthy patients with panic disorder and normal controls. Therefore, we firstly aimed to show an association between PWD and a state of high sympathetic tone such as that seen in panic disorder. We hypothesized that PWD would be higher in the patients because of the persistent anxiety and putative chronic autonomic imbalance associated with panic disorder.

METHODS AND MATERIALS

Study Population

The study comprised 40 consecutive outpatients with panic disorder (24 women and 16 men) who had applied to the Firat University School of Medicine Departments of Psychiatry and Cardiology between March and May 2006 and had been diagnosed with panic disorder according to Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (3). The control group included 40 physically and mentally healthy volunteers (22 women and 18 men). The study was conducted after approval by the Firat University School of Medicine Ethics Committee, in accordance with the Helsinki Declaration.

Each patient underwent a detailed diagnostic evaluation by one trained psychiatrist. The patients with any kind of comorbid psychiatric disorder were excluded. DSM-IV diagnoses of depressive disorder were established on the basis of independent clinical interviews by using the Structured Interview for DSM-IV, Outpatient Form (SCID-OP) (10). All patients were free of all medications at least in the previous two weeks. None of the study participants was receiving either vasoactive or psychotropic (e.g., antipsychotics, anxiolytics) agents, and none consumed alcohol or drugs. Participants were excluded if they had current or previous evidence of congestive heart failure, a recent (≤ 2 months) myocardial infarction, coronary artery by-pass grafting or percutaneous coronary intervention, another significant cardiac condition

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Received for publication August 31, 2006; revision received December 5, 2006.

DOI: 10.1097/PSY.0b013e3180616900

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(including cardiomyopathy, valvular heart disease, arrhythmias, a pacemaker, left bundle-branch block, or Wolff-Parkinson-White syndrome), a resting blood pressure higher than 180/120 mm Hg, a resting left ventricular ejection fraction <30%, a left main coronary artery stenosis \geq 50%, a serious pulmonary condition, a severe systemic illness (e.g., cancer), or a noncardiac medical illness that could influence autonomic functioning (e.g., epilepsy).

In order to reduce emotional distress or state anxiety during ECG recording, all recordings were performed in the same quiet room during spontaneous breathing, following 10 minutes of rest and adjustment period in the supine position. Moreover, in an attempt to avoid the possible influence of diurnal variations, all the recordings were performed between 9:00 AM and 12:00 PM (11).

The Panic Agoraphobia Scale (PAS) (12) and the Hamilton Depression Rating Scale (HDRS) (13) were scored concomitantly.

P-wave Dispersion Analysis

A 12-lead surface ECG was obtained from all subjects in the supine position by using a Nihon Kohden (Tokyo, Japan) machine. All patients were breathing freely but were not allowed to speak during the ECG recordings. The ECGs were recorded at a paper speed of 50 mm/s. Measurement of P-wave duration is highly important. It was reported that making an ECG record at 50 mms paper speed facilitated PWD measurement (7). Three leads were recorded simultaneously. Two investigators without knowledge of the patients' clinical statuses measured the P-wave durations manually. To improve accuracy, measurements were performed with calipers and magnifying lens for defining the ECG deflection (7–9). Higher calibration was not needed to determine the onset and offset of P waves. The onset of the P wave was defined as the junction between the isoelectric line and the start of P-wave deflection, and the offset of the P waves as the junction between the end of the P-wave deflection and the isoelectric line (7,14,15). Pmax in any of the 12-lead surface ECGs was calculated and used as a marker of prolonged atrial conduction time. P-wave dispersion, defined as the difference between Pmax and Pmin, was calculated from the 12-lead ECG.

Statistical Analysis

Statistical analysis was performed using the statistical package for social sciences (SPSS/PC 9.05 version, 1998, Chicago, IL). In the statistical analysis, Student's *t* test and Pearson's method of correlation were used. Differences were considered significant at $p < .05$ for all these tests.

RESULTS

Fourty patients (24 women and 16 men) were enrolled in this study. The control group ($n = 40$) had 22 women and 18 men. There were no significant differences in age, women to men ratio, and smoking status (rate and duration) between the patients and controls. The mean duration of illness for the patient group was 6.36 ± 3.56 years (Table 1).

The electrocardiographic data are summarized in Table 1. The left atrium (LA) sizes were not significantly different between groups ($p = .65$). Both Pmax and Pmin were significantly higher than those of healthy controls ($p < .001$ for Pmax and $p = .002$ for Pmin). PWD was significantly greater in the panic disorder group than in the controls ($p < .001$). As expected, the mean score on PAS was significantly higher for the panic disorder group than for the controls (34.8 ± 11.9 vs. 4.5 ± 5.6 , respectively; $p < .001$). Age at onset of panic disorder (21.9 ± 5.2 years) correlated negatively with the PAS scores ($r = -0.50$, $p = .026$). Heart rate did not differ significantly between the groups ($p = .69$). HDRS scores for the patient group (8.7 ± 3.9) did not correlate significantly

TABLE 1. Participant Characteristics

	Patients ($n = 40$)	Controls ($n = 40$)	<i>p</i> Value
Age (range)	31.2 ± 9.3	33.7 ± 8.6	.67
Sex ratio (female/male)	24/16	22/18	.58
Duration of illness (years)	6.36 ± 3.56	—	—
PAS score	34.8 ± 11.9	4.5 ± 5.6	<.001
HDRS score	8.7 ± 3.9	6.8 ± 2.4	.63
Pmax (ms)	93.7 ± 10.21	67.9 ± 7.41	<.001
Pmin (ms)	39.7 ± 6.35	31.1 ± 5.4	.002
PWD (ms)	54.0 ± 6.40	37.4 ± 7.21	<.001
LA size (mm)	35.6 ± 2.3	35.9 ± 2.5	.65
EF (%)	60.5 ± 3.7	60.1 ± 3.4	.73
Number of panic attacks (within last 4 weeks)	2.4 ± 1.7	—	—

Unless otherwise indicated, the values are given as mean \pm SD (range). PAS = Panic Agoraphobia Scale; HDRS = Hamilton Depression Rating Scale; PWD = P-wave dispersion; LA = left atrium; EF = ejection fraction.

with their ECG or demographic data, or with their PAS scores. Near significant correlation was found between duration of the disorder and PWD values ($r = 0.42$, $p = .07$). The PAS scores were significantly correlated with PWD for the patient group ($r = 0.47$, $p = .037$).

DISCUSSION

The present study evaluating PWD in patients with panic disorder showed the following important preliminary findings: a) both Pmax and Pmin were significantly higher than those of healthy controls; b) PWD was significantly greater in the panic disorder group than in the controls; c) the mean score on PAS was significantly higher for the panic disorder group than for the controls and correlated significantly with PWD; and d) near significant correlation was found between duration of the disorder and PWD values.

To date, there have been only limited studies on anxiety disorders in which cardiac parameters were evaluated. Nahshoni et al. (11) assessed QT wave dispersion (QTd) dispersion in 16 physically healthy and nondepressed outpatients with long-term social phobia and in 15 physically and mentally healthy age- and gender-matched controls as a marker of anxiety-induced cardiac dysregulation and found that QTd and rate-corrected QTd were significantly higher in the patients with social phobia compared with in the controls, and highly correlated with the two Liebowitz Social Anxiety Scale subscores and concluded that prolonged social phobia may be associated with an increase in QTd. The investigations revealed that excessive anxiety in physically healthy subjects is associated with a cardiac autonomic imbalance and increases the risk of coronary heart disease (16). On the other hand, panic disorder may overlap considerably with true cardiac illness and it is especially prominent in patients with documented cardiovascular disease. Morris et al. (17) evaluated the comorbidity of panic disorder with heart disease and the preva-

lence of panic disorder in 128 outpatients presenting to cardiologist. They found that 16 patients (12%) met the criteria of panic disorder, and 73 (57%) were shown to have actual cardiac illness; of these, 10 (14%) had panic disorder (17). In a prospective study of 33,999 men, the risk of sudden cardiac death was significantly related to anxiety: a multivariate odds ratio of 2.96 (18).

There are many findings of significant relations between panic disorder and cardiovascular disease for patients at last. Moving from this point, the findings obtained from the present study implicate a cardiac autonomic imbalance in patients with panic disorder. Moreover, the fact that we demonstrated a positive correlation between PWD and the severity of panic symptoms, as measured by PAS, further supports the importance of increased chronic anxiety on cardiac autonomic regulation. In addition, Tükek et al. (19) reported that increased sympathetic activity causes a significant increase in PWD. Uyarel et al. (20) reported that PWD increased in anxious situations and attributed this to increased autonomous tone. In panic disorder, sympathetic nervous system activation leads to disabled autonomic disequilibrium by increasing catecholamine (21). In addition, these increased levels of catecholamine may cause atrial fibrosis and different atrial conductions, leading to increased PWD in surface ECGs. PWD not only correlated significantly with symptom severity at the time of the investigation, but also with the chronicity of the disorder. Therefore, we can see an ongoing autonomic imbalance, and conclude that PWD may be a state marker of panic disorder. However, to support this notion, a long-term follow-up investigation, in which PWD values are screened at different times throughout the course of the disorder, should be performed. It has been suggested that prolongation of P-wave duration is an accepted indicator of an interatrial conduction disturbance that can occur independently of an increase in atrial size (22). Moreover Dilaveris et al. (7) reported that left atrial maximal diameter is not a significant predictor of AF episodes. Ishimoto et al. (23) reported that there is no correlation between filtered P-wave duration and atrial enlargement. In addition, it has been suspected that P-wave prolongation might be caused in part by abnormalities in atrial electrical properties, such as intra-atrial or interatrial conduction disturbance or block (24). In contrast, some investigators (25, 26) reported that the left atrial diameter is a significant predictor of AF episodes. There were no differences between the patients and the controls in regard to left atrial diameters. This supports the notion that PWD prolongation may be associated with increased sympathetic tone.

The present study has some limitations. First, our sample size was small and preliminary, further studies that compare ANS function across various subgroups of panic disorder determined that duration of illness, severity of symptoms, treatment response, or other factors might provide a more detailed role of the ANS in the pathophysiology of panic disorder. Secondly, electrocardiographical measurements

were performed using a 10x lens, not using computer programming. In addition, electrophysiological evaluation was not performed. Finally, the patients were not followed up longitudinally regarding mortality and morbidity.

In conclusion, our results suggest that PWD may be associated with panic disorder; though our sample is too small to allow us to obtain a clear conclusion. Future studies with larger samples evaluating the effects of treatment are required.

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