The prediction of nonresponse to pharmacotherapy in panic disorder
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Chapter 6

Five minute recordings of heart rate variability in obsessive compulsive disorder, panic disorder and healthy volunteers

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Submitted
Abstract

Background: Recent studies have used spectral analysis of heart rate variability (HRV) to study autonomous nervous system (ANS) function in panic disorder (PD). Most studies reported a reduced HRV in resting PD patients, suggesting increased sympathetic and decreased parasympathetic tone. In obsessive compulsive disorder (OCD) inconsistent findings have been reported on ANS function and to date no studies have been carried out with spectral analysis of HRV. In this HRV study we compared ANS function in patients with PD, OCD and normal controls.

Methods: Standardized HRV measurement was carried out in 24 PD patients, 26 OCD patients and 24 age matched normal controls. All patients were drug free. As this comparison yielded unexpected results, the PD and normal control samples were enlarged to 53 and 54 subjects, respectively, to verify our first measurement.

Results: OCD patients were not characterized by a reduced HRV, as compared to normal controls. This was also found in PD patients, even in the enlarged sample.

Conclusions: HRV analysis in patients with OCD or PD showed that these patients were not characterized by ANS abnormalities, as no evidence was found of diminished HRV in a large sample of resting OCD and PD patients, measured sitting on a hospital bed.
**Introduction**

In all anxiety disorders, symptoms are present which suggest the involvement of the autonomous nervous system (ANS). In panic attacks, which can occur in several anxiety disorders, ANS symptoms are prevalent, such as palpitations, chest pain and shortness of breath. In panic disorder (PD), which is characterized by spontaneous panic attacks (American Psychiatric Association 1994), several studies have investigated the involvement of the ANS (Roth et al 1986; Weissman et al 1987; Yeragani et al 1989; Katerndahl 1990; Papp et al 1993; Seier et al 1997; Bystritsky et al 2000).

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 regulatory processes that maintain cardiovascular system stability (Appel et al 1989; van Ravenswaaij-Arts et al 1993). HRV is primarily controlled by the continuous interplay of the sympathetic and parasympathetic (vagal) branches of the ANS (Friedman and Thayer 1998b). Spectral analysis of HRV quantifies the relative influence of each branch on heart rate (HR), as these rhythms occur at different frequencies. Two frequency bands are usually distinguished: the high frequency band (HF: around 0.25 Hz) is thought to be mediated by cardiac vagal tone, which depends on respiration, and a low frequency band (LF: around 0.10 Hz) which is mediated by both branches of the ANS (Akselrod et al 1981; Pomeranz et al 1985). The ratio of LF power to HF power (LF/HF) is commonly seen as an index of cardiac sympathovagal balance (Pagani et al 1986).

In several studies it has been reported that PD patients are characterized by a reduced HRV, reduced HF power, increased LF or an elevated LF/HF ratio; for an extensive review see Friedman and Thayer (1998b). These HRV abnormalities seem to point to a disturbed balance between the vagal and the sympathetic branches of the ANS, with possible vagal hypoactivity and sympathetic overactivity.

Not all studies have consistently shown this pattern: one research group reported no HRV abnormalities in PD patients (Stein and Asmundson 1994; Asmundson and Stein 1994). Possible explanations mentioned for these discrepant findings were factors such as apprehensiveness of subjects at the time of testing (Ito et al 1999), age, fitness, illness duration and illness severity (Stein and Asmundson 1994; Asmundson and Stein 1994), or even methodological differences in the analysis of HRV (Friedman and Thayer 1998b).

HRV has not been investigated very thoroughly in other anxiety disorders. To date, no studies in Obsessive Compulsive Disorder (OCD) have been carried out, using spectral analysis of HRV. Patients with OCD are characterized by intrusive thoughts and irresistible urges to perform ritualized actions. When patients attempt to control these thoughts and urges, anxiety is often reported and elevated ANS activity is evident (Boulougouris et al 1977; Rabavilas et al 1977; Zahn et al 1996). Earlier studies on ANS functioning in OCD patients have shown conflicting results: some studies found higher levels of skin conductance or heart rate, indicative of elevated autonomic arousal (Insel et al 1985; Benkelfat et al 1991), whereas others found no differences with healthy controls (Hollander et al 1991).
In OCD three studies have investigated baseline differences in heart inter-beat intervals (IBI’s) as a marker of ANS function. Hoehn-Saric and coworkers (1995) could not find baseline differences in IBI’s between adult OCD patients and controls. They did find that OCD patients showed an nonspecific decreased physiological flexibility on provocation with two stressful psychological tasks. McCarthy and coworkers (1995) used an intake-rejection attentional paradigm to compare heart rate activity between OCD patients and high and low trait anxious controls. IBI’s, measured at baseline and during tasks, did not differ between the groups. Zahn et al (1996) measured autonomic changes during rest, mild stress periods and a signal detection task in a substantial group of children and adolescents with OCD. They were unable to find evidence for a specific dysfunction in HRV underlying childhood OCD.

One might conclude that ANS dysfunction is not a prominent feature of OCD, but this conclusion seems premature. A methodological flaw in the studies discussed above is that the authors reported on mean IBI’s, measured at baseline, as a marker of ANS function. Mean IBI’s, or mean heart rate, do not yield much information on the functioning of the ANS. They do offer information on autonomic arousal when used as a measure before and after a provocation of the ANS (Porges and Bohrer 1990). Therefore, spectral analysis of HRV is needed in order to quantify the effect on heart rate of both branches of the ANS, and thus ANS functioning.

In the present study we compared ANS system functioning in PD patients, OCD patients and normal controls. This was done by means of five-minute recordings of HRV, analysed with spectral analysis, with subjects sitting on a hospital bed. Because of the lack of consistency in reports on ANS dysfunction in OCD, we hypothesized that OCD patients do not differ from normal controls, matched on age. Furthermore, we expected to replicate earlier findings of reduced HRV in PD patients, as compared to normal controls.

As this comparison yielded unexpected results, we performed a second comparison, with substantially larger groups of PD patients and normal controls, to verify our first measurement.

Methods

subjects: comparison I

For the comparison of HRV data of PD patients, OCD patients and normal controls, the HRV data was pooled of two studies, which are published separately (Boshuisen et al 2001; Nielen et al 2001), together with a set of measurements in normal controls, matched on age. Pooling data was straightforward, as all HRV measurement and subsequent analyses were carried out using the same protocol, as described below. Only subjects with valid HRV data were used in the pooled data set: data of four PD patients was not included, three because of hardware failure, one because of unstable data (>8% interpolation). HRV data of one OCD patient and one normal control subject was not included because of hardware failure.
The PD patient sample consisted of 24 patients suffering from panic disorder with or without agoraphobia. These patients participated in an open label treatment study with mirtazapine (Boshuisen et al. 2001). Subjects (8 males; 16 females) were included if they fulfilled the DSM-IV (American Psychiatric Association 1994) criteria of panic disorder with (n = 16) or without agoraphobia (n = 8), with the additional requirement of having experienced at least three panic attacks in the three weeks prior to study. The age of the subjects ranged from 24 years to 60 years (mean ± SD = 39.9 ± 10.8). The HRV measurement took place before the start of treatment. All subjects were free from psychoactive medication for at least 2 weeks prior to the measurement (four weeks in the case of fluoxetine). The only allowed concomitant psychoactive medication was oxazepam (20 mg daily for 3 days at most).

The OCD patient sample consisted of 26 patients. These patients participated in a neuropsychological study on cognitive functioning (Nielen et al. 2001). Subjects (7 males; 19 females) were included if they fulfilled the DSM-IV criteria of obsessive-compulsive disorder (American Psychiatric Association 1994). The age of the subjects ranged from 22 years to 52 years (mean ± SD = 37.4 ± 9.4). All patients were drug free for at least four weeks prior to the measurement.

The normal control group consisted of 24 subjects (10 males; 14 females). The age of the subjects ranged from 26 years to 59 years (mean ± SD = 39.6 ± 10.0). Control subjects had no known diagnosable medical or psychiatric conditions.

For the comparison HRV in a larger sample, data of PD patients and normal controls was again pooled and matched on age. The HRV data of the PD patients described above was reused, together with HRV data of an ongoing study in PD. Patients participating in this open label treatment study with sertraline had to fulfill similar inclusion and exclusion criteria as in the study of Boshuisen et al. (2001). The HRV measurement also took place before the start of treatment and all subjects participating in the sertraline study were free from psychoactive medication for at least 2 weeks prior to the measurement. The only allowed concomitant psychoactive medication was oxazepam (20 mg daily for 3 days at most). This pooling resulted in a total PD sample of 53 patients (24 males; 29 females). Twenty-nine subjects fulfilled the DSM-IV (American Psychiatric Association 1994) criteria of panic disorder with agoraphobia; twenty-four subjects suffered from panic disorder without agoraphobia. The age of the subjects ranged from 24 years to 61 years (mean ± SD = 40.2 ± 10.3).

The HRV data of normal controls was reused in this comparison and a further 30 subjects were measured. This resulted in a total sample of 54 subjects (20 males; 34 females). The age of the subjects ranged from 23 years to 61 years (mean ± SD = 39.4 ± 10.0). The HRV data of two patients from the study with sertraline and one normal control subject was not used, because of hardware failure.
The following exclusion criteria were used in both patient studies: any present primary psychiatric diagnosis, other than panic disorder or obsessive-compulsive disorder, medical or neurological problems, a score $\geq 15$ ($\geq 16$ in the OCD study (Nielen et al 2001)) on the Hamilton Depression Scale (HDS: (Hamilton 1967)), significant Axis II presence, alcohol or substance abuse within the last 2 years.

All patients referred themselves to the Anxiety Research Clinic of our hospital. Normal controls were recruited by newspaper advertisements. All subjects signed an Informed Consent Form prior to admission. This study was approved by the Medical Ethics Committee of the Academic Hospital Groningen.

**experimental procedure**

Heart rate variability was measured in our lab using a standardized procedure. Before the actual measurement, the equipment was shown to the subjects and the procedure was explained to them. The subject would then sit on a hospital bed and the equipment would be connected. The ECG was measured using three Ag-AgCl electrodes. Respiration was measured with a Pneumotrace (UFI, Morro Bay, USA) around the upper thorax, near the eleventh rib. The ECG and respiration signals were led to an A/D card (PCL-812) in a PC (80486, 66 MHz). The data acquisition was performed by the MPOLY computer program (Inspector Research Systems, Amsterdam, the Netherlands). The sampling frequency was 100 Hz. The sampled data was stored on disk for off-line analysis.

After a 10 minute period of acclimatization of the person the actual measurement began. During a 6 minute interval subjects were instructed to breathe normally and to refrain from talking. During the measurement, the experimenter was in the same room, but out of direct sight from the subject.

The off-line analysis started with visual inspection of the ECG for artifacts, such as premature ventricular beats, electrical “noise” or aberrant beats, and was carried out on all HRV data. R-peaks in the ECG were detected by software, with an accuracy $\pm 2$ ms, based on an interpolation algorithm. Artifacts were eliminated and the resulting gaps were interpolated. When a data set had more than 5% interpolated R-R intervals, the data was considered unstable and discarded. Artifact processing and power spectral analysis of the HR data were performed with the package CARSPAN 2.0 (IECProgamma, Groningen, the Netherlands), which is a software package specifically designed for cardiovascular spectral analysis. Spectral power was calculated for the following bands: total spectrum power (TP: 0.02 – 0.50 Hz), low frequency power (LF: 0.02 – 0.15 Hz) and high frequency power (HF: 0.15 – 0.5 Hz). The ratio between LF and HF was also calculated. Power values (calculated as ms$^2$) were log-transformed before they were used in the statistical analysis.
statistical analysis

All data was entered into an SPSS database. An $\alpha$ of 0.05 was used for all statistical analyses. The EXPLORE procedure was used to inspect data for outliers. Differences between the groups were analysed using ANOVA. For the analysis of differences in HRV parameters, the time of the HRV measurement was used as covariate, since this variable differed between groups (Comparison I: $F = 22.4$, df = 2,67, $p < 0.001$; Comparison II: $F = 4.2$, df = 1,101, $p = 0.04$). For the analysis of TP, LF and HF age was also used as covariate, as these HRV parameters decline with age (TP, LF, HF: Comparison I: Pearson’s $r = -0.53$, -0.50, -0.49; Comparison II: Pearson’s $r = -0.44$, -0.37, -0.46; all correlations $p < 0.001$).

When the assumption of normality was violated a non-parametric Kruskal-Wallis test was carried out.

Results

Comparison I

Normal controls were measured at a later time of day, as compared to PD and OCD patients (Table 1). The time of day did not have any influence on the HRV parameters (Pearson’s $r < 0.1$).

The analysis of variance, with time of measurement and age as covariates, of heart rate and the HRV parameters yielded no statistically significant differences between the groups.

Comparison II

The larger sample comparison of PD patients (n = 53) and normal controls (n = 54) yielded similar results to Comparison I (Table 1). Again no statistically significant differences were found. The LF/HF ratio of PD patients appeared larger than the ratio of normal controls and this difference even approached statistical significance ($p = 0.081$). The EXPLORE procedure of SPSS revealed that one outlier (a PD patient with a LF/HF ratio 4.7 standard deviations above the mean) was partly responsible for this difference. Removal from the analysis of this outlier resulted in a mean (± SD) LF/HF ratio of 1.6 (± 1.7).

Visual inspection of the scatterplot of HF power versus age (Figure 1), with separate markers for PD patients and normal controls, shows an even distribution of HF power values over the groups, and a steady decline of HF power with age.

Discussion

To our knowledge, this is the first study which investigated HRV, by means of spectral analysis, in OCD patients. The main finding in this study was that mean heart rate and HRV parameters of OCD patients do not differ from normal controls. To our surprise this was
also the case in PD patients, who did not differ from normal controls, even in a large sample.

As hypothesized, resting OCD patients were not characterized by HRV abnormalities in our static measurement of HRV functioning. Mean heart rate was also not different from normal controls. These findings support the notion that OCD patients are not characterized by ANS dysfunction or autonomic hyperarousal, and they are thus in concordance with the three studies which used IBI’s as a measure of HRV (Hoehn Saric et al 1995; McCarthy et al 1995; Zahn et al 1996). The use of spectral analysis has shown that the influence of the sympathetic and parasympathetic branches of the autonomous nervous system on heart rate is not different in OCD patients, while at rest and as compared to normal controls.

In our study, subjects were measured at rest: no patient complained of anxiety or, in the case of OCD, the urge to ritualize in the measurement setting. To the experimenters (MMAN or BRS) no overt signs of unease or anxiety were apparent. The finding that the mean heart rate of PD and OCD patients were not elevated, as compared to controls, corroborates our opinion that patients were truly at rest.

From the literature on PD it is known that anxiety or even panic attacks can arise from a period of relaxation (Cohen et al 1985; Adler et al 1987; Knott et al 1997; Roth et al 1998). An explanation for this phenomenon might be that PD patients constantly fear the occurrence of spontaneous panic attacks. Once a PD patient tries to relax, the absence of external distraction from fearful somatic sensations, such as a pounding heart, may precipitate an attack. One might expect that PD patients, while undergoing an HRV measurement where they are measured at rest, are prone to these relaxation induced panic attacks. In our study, however, no patient reported a panic attack. This is in concordance with the literature on spectral HRV analysis in PD, where no panic attacks during the HRV measurement have been reported (Yeragani et al 1993; Middleton et al 1994; Rechlin et al 1994; Klein et al 1995; Tucker et al 1997; Friedman and Thayer 1998a; Ito et al 1999; Cohen et al 2000). It appears a discrepancy exists between HRV studies in PD, where no patient panics while at rest, and the studies on relaxation induced panic attacks.

There were no differences in heart rate or HRV parameters in PD patients, as compared to normal controls, measured at rest and sitting on a hospital bed. The likelihood that this is a Type II error (false-negative) is diminished by the relatively large sample size. To the author’s knowledge, this study has included the largest sample ever studied by spectral HRV in PD. We could not replicate findings of a diminished HRV in PD patients measured at rest, as reported by other groups that used spectral analysis (Yeragani et al 1993; Middleton et al 1994; Rechlin et al 1994; Klein et al 1995; Tucker et al 1997; Friedman and Thayer 1998a; Ito et al 1999; Cohen et al 2000). What typically has been reported in these studies is reduced HF power (Friedman and Thayer 1998a; Cohen et al 2000), increased LF power (Middleton et al 1994; Rechlin et al 1994; Ito et al 1999; Cohen et al 2000) and an elevated LF/HF ratio (Klein et al 1995; Tucker et al 1997; Friedman and Thayer 1998a). A closer inspection of these findings reveals that some groups reported a diminished HRV in resting PD patients, measured in a supine (Yeragani et al 1993; Rechlin et al 1994; Klein et al 1995;
Cohen et al (2000) or reclining (Tucker et al 1997) position, whereas others found no differences in resting PD patients, measured in a supine (Ito et al 1999) or semisupine (Middleton et al 1994) position. These studies did report HRV abnormalities with patients standing (Middleton et al 1994), or during head-up tilt (Ito et al 1999). Thus, controversial findings were reported previously. Moreover, two published studies (Stein and Asmundson 1994; Asmundson and Stein 1994) reported that PD patients did not differ from normal controls on a variety of ANS function tests. These studies did not use spectral analysis of HRV, but these were methodologically sound studies with relatively large samples of patients and age matched controls.

A matter of some debate might be whether a static measurement of HRV in resting subjects, sitting on a hospital bed, is the ideal method of investigating ANS functioning. From the literature on spectral analysis of ANS functioning it is known that posture has considerable influence on HRV: the HF component is most prominent in supine subjects and is decreased, relative to the LF component, during upright tilt and in standing subjects. Likewise, the LF component is enhanced during upright tilt or in standing subjects (Pomeranz et al 1985; Weise et al 1987; Schondorf 1993). Since PD patients are postulated to be characterized by increased LF power, decreased HF power and an increased LF/HF ratio, HRV measurements in supine, semisupine (sitting on a bed) or standing subjects should reveal these differences. It therefore seems unlikely that the posture of our subjects could explain why we could not replicate earlier findings.

A series of dynamic autonomic function tests, such as the Valsalva maneuver and cold pressor testing, analysed with spectral analysis, in a sufficiently large sample, should reveal whether the postulated ANS abnormalities of PD patients are only apparent under certain well circumscribed conditions. This, in fact, would imply a replication of the study of Stein and coworkers (1994), who used an extensive battery of autonomic tests, but presented their negative study without spectral analysis.

A methodological flaw of this study is the fact that not all HRV measurements took place at the same time. We statistically corrected for the different times of measurement in our analyses, at the expense of one degree of freedom. Hardware failure resulted in a total of eight missed measurements. Given the large sample size and the total absence of even a trend towards a statistically significant result, it seems unlikely that the loss of one degree of freedom or the missed measurements could have made any difference.

In conclusion: On the basis of this study, one can only conclude that OCD and PD patients are not characterized by ANS abnormalities, as no evidence was found of diminished HRV in a large sample of resting OCD and PD patients, measured sitting on an hospital bed.
References


Boshuisen ML, Slaap BR, den Boer JA (2001): The effect of mirtazapine in panic disorder, an open label pilot study with single blind placebo run in period. (Submitted for publication)


Table 1: Baseline mean (± SD) values of time of measurement, heart rate and HRV parameters in Panic Disorder, Obsessive Compulsive Disorder, and normal controls (Comparison I); Panic Disorder and normal controls (Comparison II)

<table>
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<tr>
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<th>Comparison I</th>
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<th>Comparison II</th>
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<tbody>
<tr>
<td></td>
<td>PD (n = 24)</td>
<td>OCD (n = 26)</td>
<td>NC (n = 24)</td>
<td>PD (n = 53)</td>
</tr>
<tr>
<td>HR</td>
<td>72.4 (± 12.9)</td>
<td>71.6 (± 10.7)</td>
<td>66.3 (± 9.3)</td>
<td>70.2 (± 10.4)</td>
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<tr>
<td>TP</td>
<td>6.9 (± 1.3)</td>
<td>7.3 (± 0.8)</td>
<td>7.3 (± 1.4)</td>
<td>7.1 (± 1.2)</td>
</tr>
<tr>
<td>LF</td>
<td>5.9 (± 1.4)</td>
<td>6.4 (± 0.9)</td>
<td>6.5 (± 1.5)</td>
<td>6.3 (± 1.3)</td>
</tr>
<tr>
<td>HF</td>
<td>5.9 (± 1.5)</td>
<td>6.3 (± 1.1)</td>
<td>6.3 (± 1.6)</td>
<td>6.1 (± 1.4)</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.6 (± 1.8)</td>
<td>1.8 (± 2.0)</td>
<td>1.5 (± 1.1)</td>
<td>1.9 (± 2.4)</td>
</tr>
</tbody>
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Legend: Time = mean time point of the HRV measurement; HR = heart rate; TP = total spectrum power; LF = low frequency power; HF = high frequency power; LF/HF = low frequency / high frequency power ratio; $^1$ Log-transformed power value in ms²
Figure 1: High Frequency (HF) power and age in Panic Disorder patients and normal controls