Major Depression with Ischemic Heart Disease: Effects of Paroxetine and Nortriptyline on Long-Term Heart Rate Variability Measures

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Background: *Studies have linked depression to sudden death and serious cardiovascular events in patients with preexisting cardiac illness. Recent studies have shown decreased vagal function in cardiac patients with depression and depressed patients without cardiac illness.*

Methods: *We compared 20-hour, sleeping, and awake heart period variability measures using spectral analysis, fractal dimension, and symbolic dynamics in two patient groups with major depression and ischemic heart disease (mean age 59–60 years) before and after 6 weeks of paroxetine or nortriptyline treatment.*

Results: *Spectral measures showed decreases in awake and sleeping total power (TP: 0.0–0.5 Hz), ultra low frequency power (ULF: 0–0.0033 Hz), very low frequency power (VLF: 0.0033–0.04 Hz), and low-frequency power (LF: 0.04–0.15 Hz) for nortriptyline condition and a decrease in high-frequency power (HF: 0.15–0.5 Hz) for the awake condition in patients who received nortriptyline. A measure of nonlinear complexity, WC-100, significantly increased after paroxetine during the awake condition.*

Conclusions: *These findings suggest that nortriptyline has stronger vagolytic effects on cardiac autonomic function compared with paroxetine, which is in agreement with previous clinical and preclinical reports. Paroxetine may have some cardio-protective effects, especially in cardiac patients.* Biol Psychiatry 2002;52:418–429 © *2002 Society of Biological Psychiatry*

Key Words: Major depression, cardiovascular mortality, nonlinear, spectral analysis, symbolic dynamics, heart rate variability, awake, sleep

Introduction

Recently major depression has been linked to poor prognosis in patients with heart disease (Carney et al 1993, 1995, 1997; Dalack and Roose 1990; Everson 1998; Frasure-Smith et al 1993; Horrobin and Bennett 1999; Musselman 1998), and some studies have shown decreased heart rate variability (HRV) in these vulnerable patients with and without overt cardiac disease (Krittiyaphong et al 1997; Stein et al 2000; Yeragani 2000). One study suggested that negative feelings were associated with arterial wall thickening (Agewall 1996).

Roose et al (1998, 1999) have reported that nortriptyline was associated with a higher rate of side effects compared with paroxetine in depressed patients with heart disease. Although it is not directly relevant, several articles have dealt with the issue of sudden cardiac death in children who were placed on tricyclics such as desipramine and the effects of these agents on cardiac autonomic function (Biederman et al 1993; Mezzacappa et al 1998; Walsh et al 1994; Werry et al 1995). Together these findings underscore the importance of choosing an antidepressant that has a favorable cardiac side-effect profile. Some of the recent noninvasive techniques such as HRV and QT interval variability are valuable tools to study the effect of various antidepressants in patients with major depression. An increase in cardiac sympathetic function or a decrease in vagal function can lead to serious ventricular arrhythmias and sudden death (Rozanski et al 1988). Recent noninvasive techniques on heart rate (HR) and QT interval variability show a great deal of promise to study cardiac autonomic function in different disorders and also to evaluate the effects of various drugs (Atiga et al 1998; Berger et al 1997; Malik and Camm 1990; Malliani et al 1991; Yeragani 1995; Yeragani et al 1993a, 2000b, 2000c). Although Yeragani et al (1991) did not find significant differences in time domain measures of 5-min segments of heart rate between control subjects and patients with major depression, their findings on 24-hour HRV and measures of nonlinearity and chaos suggest that these patients appear to have a relative decrease in cardiac

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vagal function (Yeragani et al 2002a). In fact, in a recent report, Yeragani et al have shown highly significant differences in largest Lyapunov exponent (LLE), a measure related to cardiac vagal function in patients with panic disorder (Radhakrishna and Yeragani, in press). They also showed that word count (WC-100), a measure derived from symbolic dynamics, was significantly lower in these patients with anxiety, which also relates to nonlinear complexity of the time series (Yergani et al 2000a). This is important in view of the strong association between decreased HRV and significant cardiovascular mortality in patients with cardiac disease, depression, anxiety and also in normal control subjects (Bigger et al 1992; Kawachi et al 1994; Kleiger et al 1987; Molgaard et al 1991).

Spectral analysis of long-term HR or heart period (HP) time series can be used to obtain powers in frequency bands such as ultra low frequency power (ULF: 0–0.0033 Hz), very low frequency power (VLF: 0.0033–0.04 Hz), low-frequency power (LF: 0.04–0.15 Hz), and high-frequency power (HF: 0.15–0.5 Hz). High-frequency power is related to respiratory sinus arrhythmia, thus reflecting cardiac vagal function, whereas LF power is mediated dually by vagal and sympathetic systems (Akselrod et al 1981; Lindqvist et al 1990; Pomeranz et al 1985). Although controversial, some investigators have used the LF/HF ratios as indicative of sympathovagal interaction (Cacioppo et al 1994; Pagani 1986). The mechanism is not clearly understood, but ULF and VLF may also be mediated by sympathetic, rennin-angiotensin, and thermoregulatory mechanisms (Bonaduce et al 1994; Lindqvist et al 1990; Niemela et al 1994).

Previous studies suggest that tricyclic antidepressants (TCAs) result in tachycardia, prolongation of QTc interval, decreased HRV, and an increase in QT variability (Georgatas et al 1987; Glassman and Bigger 1981; Glassman et al 1987; Roose and Glassman 1989; McLeod et al 1992; Yeragani et al 1992, 2000c), which are all associated with significant cardiovascular events. Rechlin (1994) showed that amitriptyline significantly decreases HRV in patients with depression. On the other hand, Tucker et al (1997) reported that paroxetine increased cardiac vagal activity in patients with panic disorder; however, our previous findings on paroxetine in patients with panic disorder in their 30s have shown a decrease of cardiac vagal function as suggested by a decrease of high-frequency power of HR (Yeragani et al 1999).

Several investigators have demonstrated the nonlinear nature of the HR or HP time series and have also shown the additional utility of these measures to the traditionally used time and frequency domain measures (Braun et al 1998; Curione et al 1998; Ganz et al 1993; Glenny et al 1991; Goldberger and West 1987; Guzzetti et al 1996; Ho et al 1997; Kaplan et al 1991; Lipsitz and Goldberger 1992; Lombardi et al 1996; Pincus et al 1991; Radhakrishna et al 2000; Radhakrishna and Yeragani, 2001; West and Goldberger 1987; Yeragani et al, 2002a, 2002b). Although there are numerous techniques to quantify nonlinearity, complexity, predictability, and chaos, these techniques need further evaluation as to what exactly they represent in terms of physiologic significance and their relationship to a particular cardiac condition. Poon and Merrill (1997) reported a decrease of cardiac chaos in severe congestive heart failure, a condition associated with sudden death. Voss et al (1996, 1998) showed that nonlinear measures seem to be a better predictor of high arrhythmia risk than just the global heart rate variability using multiparametric analysis. Makikallio et al (1999) showed that fractal analysis of HR could be used as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction (MI). Huikiuri et al (1999, 2001) discussed the time, frequency domain, and the nonlinear measures in their reports and suggested that the nonlinear measures of HR variability are promising tools to stratify risk and as predictors of death and life-threatening arrhythmias in postinfarction populations. Thus, mounting evidence suggests that the nonlinear measures are clinically important.

It is important to understand the effects of various antidepressant drugs on cardiac autonomic function in various age groups of patients using these novel noninvasive techniques. In this study, we sought to investigate the effects of paroxetine and nortriptyline in patients with major depression and ischemic heart disease aged about 60 years using HPV and Holter electrocardiograph (ECG) records obtained in a previous treatment study (Roose et al 1998). In this study, Roose et al found that 61% of patients on paroxetine and 55% on nortriptyline improved after treatment. There was no significant change in blood pressure or conduction intervals on ECG with either drug. Paroxetine had no sustained effects on heart rate or rhythm; however, nortriptyline produced a significant increase in HR and a decrease in standard deviation (SD) of all normal R–R intervals. Nortriptyline produced adverse cardiac events in 18% of patients compared with only 2% of patients in the paroxetine group.

We used frequency domain measures and also measures of symbolic dynamics (Voss et al 1996; Yeragani et al 2000a), which reflects the nonlinear complexity of these time series and one method of computing fractal dimension (FD) (Katz 1988; Yeragani et al 1993b, 1997, 1998b). We hypothesized that nortriptyline treatment would be associated with a more significant decrease in various measures of HRV compared with paroxetine based on the previous finding of a significant vagolytic effect of nortriptyline in these patients (Roose et al 1998).

Methods and Materials

Subjects

ORIGINAL STUDY DESIGN. This study was conducted in four University research centers (Roose et al 1998) and was approved by the internal review boards at all four sites for the protection of subjects. The inclusion criteria were DSM-IV criteria for major depressive disorder, unipolar subtype, with a score of 16 or higher on the 17-item Hamilton Rating Scale for Depression (HAMD; Hamilton 1960), ischemic heart disease, and the patient's being capable and willing to sign informed consent to participate in this study aimed at the cardiovascular safety of antidepressant medication. Patients were considered to have ischemic heart disease if they had had an MI, coronary artery bypass graft surgery, or coronary angioplasty; had a positive stress test; or had angiographic evidence of a 75% or greater luminal narrowing of a major coronary artery or one of its primary branches. Patients were excluded if the MI occurred within 3 months before their recruitment, a baseline QTc of 460 msec or more, unstable or crescendo angina, or if they were receiving drugs with class I antiarrhythmic activity or warfarin.

After patients signed the informed consent, baseline cardiac testing was conducted during a 2-week placebo period, including a 24-hour continuous Holter ECG record and a routine 12-lead ECG at the beginning and end of the placebo period. At the end of the placebo period, if the patient had completed with the study procedures and continued to meet inclusion and exclusion criteria, he or she was randomized by permuted blocks of 10 to treatment with either paroxetine or nortriptyline for a double-blind 6-week trial.

DOSING. Patients aged less than 65 years received an initial dose of 20 mg/day of paroxetine for the first 3 weeks; older patients were started at 10 mg/day for the first week, and then the medication was increased to 20 mg/day for the next 2 weeks. At the end of 3 weeks, if patients did not show a 50% decrease in HAMD scores, the paroxetine dose was increased to 30 mg and, if necessary, to 40 mg at the end of week 5. The nortriptyline dose was started at 25 mg and increased to 50 mg by day 3. On the seventh day, plasma level was measured and the dose adjusted to achieve a plasma nortriptyline level between 304 and 456 nmol/L. The idea was to have the dose within the therapeutic range of 190–570 nmol/L (50–150 ng/mL). Medication compliance was monitored by weekly pill counts and plasma level measurements; blood samples were taken from patients on paroxetine as well.

DRUG DISCONTINUATION. Medications were discontinued if there was an adverse cardiac event, if there was a greater than 50% increase in the QRS interval from baseline, if the QRS interval exceeded 180 msec in patients with bundle-branch block at baseline, if the QTc interval exceeded 500 msec, or if a patient developed a proarrhythmic effect. Additional factors that were taken into account included cardiac enzyme levels, 24-hour ECG, and significant blood pressure changes.

CARDIAC ASSESSMENT. We obtained 24-hour ECG before and after 2 weeks of placebo administration. Patients received active medication for 6 weeks. We then repeated 24-hour ECGs at the end of 2 and 6 weeks of medication treatment. Complete data included four 24-hour ECG records.

The mean ± SD for paroxetine dose was 22 ± 5 mg/day and 74 ± 30 mg/day for nortriptyline. At week 6, the nortriptyline levels were within the therapeutic range. In the original sample, 37/41 (90%) of patients treated with paroxetine completed the trial, and 25 (68%) were responders. Sixty-five percent (26/40) completed the nortriptyline trial, and 22 (85%) were responders.

Twenty-Four Hour Heart Rate Variability

The techniques used for this study were similar to those used in our previous studies (Yeragani et al 1997, 1998a). This study included only those patients who had at least 20,000 sec of data during the awake period, pretreatment records from before placebo administration, and records from 6 weeks after treatment. Many patients did not have all these records, so we had to limit our analyses to two records; however, we compared pre- and postplacebo lead-in records and found no significant difference in any of our HRV measures. The reason to exclude the 2-week posttreatment record was that the effects of the drugs might not have been observable by then. Twenty-four patients were included in the paroxetine treatment study and 20 patients in nortriptyline study. We have used means and standard deviations throughout the text and tables of this article. Thirty-three patients had 20-hour data, 44 had awake data, and 30 had sleeping data. Age ranges of the paroxetine group for the 20-hour, awake, and sleeping data sets, respectively, were 60.4 ± 10.5, 58.0 ± 10.2, and 60.4 ± 10.5 years; for the nortriptyline group, they were 60.8 ± 13.4, 61.0 ± 13.2, and 61.6 ± 13.1 years.

Twenty-four hour ECG was recorded using cassette tapes and digitized with a Marquette 8000 scanner; QRS labeling and editing was done using standard Marquette algorithms. The ASCII files of R–R intervals in milliseconds were edited according to previous techniques that have been described in detail (Huikuri et al 1994; Yeragani et al 1997, 1998). These data were edited using software that eliminated any premature ventricular beats. This method is similar to that used by Huikuri et al (1994). An R–R interval was interpreted as a premature beat if it deviated from previous qualified interval by more than a tolerance level of 30%. These data were eliminated and the resulting gaps filled with an average value in the immediate neighborhood. The edited time series were then sampled at 2 Hz using the technique described by Berger and coworkers to obtain the instantaneous HR (Berger et al 1986). This stepwise continuous instantaneous HR signal maintains an amplitude equal to the reciprocal of the R–R interval and the convolution of the HR signal with the rectangular window has the effect on the power spectrum of multiplication by a low-pass filter. A 2-Hz sampling rate would allow an accurate estimation of the power spectrum up to 0.5 Hz, which is equivalent to a breathing rate of 30/min. From here forward, all data were converted to a R–R interval time series (60000/HR in beats per minute [bpm]). Then the data were detrended using a linear detrending technique before the other analyses except for the nonlinear analyses of FD and symbolic dynamics.

SPECTRAL ANALYSIS. The power spectrum was obtained as the magnitude squared of the Fourier transform using a rectan-

gular data window. The powers were integrated in the following bands; total power (TP): 0–0.5 Hz, ULF: 0–0.0033 Hz, VLF: 0.0033–0.04 Hz, LF: 0.04–0.15 Hz, and HF: 0.15–0.5 Hz. Relative powers were calculated as the percentages of total power in each frequency band. We include a detailed description of the methods used to calculate fractal dimension and measures of symbolic dynamics in the Appendix.

FRACTAL DIMENSION. We calculated FD according to the same method used in our previous studies (Yeragani et al 1993b, 1997, 1998b), which was originally described by Katz (1988). (See Appendix 1).

SYMBOLIC DYNAMICS. These techniques have been described in detail by Kurths et al (1995) and Voss et al (1996) and recently used in our study in patients with panic disorder (Yeragani et al 2000b). (See Appendix 1). We have also calculated the SD of the word sequence (WSDVAR-100) after transformation of the sequence by using the words 1 or 3, as suggested by Voss et al (1996). In another analysis, we obtained the symbol sequences using only 0 or 1, where 0 represents the difference between consecutive beats lower than 5, or 100 msec, and 1 represents the cases in which the difference between two successive beats exceeded this limit. We then calculated all three-digit words that contained either 000 (A) or 111 (B). We call these PN-5-A, PN-100-A and PN-5-B, and PN-100-B.

Statistical Analysis

We initially performed a three-way analysis of variance (ANOVA) with the two drug conditions as the grouping factor and the awake and sleeping periods as one repeated measure, and pre- and postdrug (first and fourth Holter sessions) values as the second repeated measure. Because there were significant differences between sleeping and awake periods, we chose to perform two-way ANOVAs separately for awake and sleeping periods. We used two-way ANOVA for repeated measures with the drug condition as the grouping factor and pre- and posttreatment (6 weeks) measures as the repeated measures. Significant effects were followed up by paired *t* tests to compare patients separately for each drug condition. All tests were two-tailed, and a probability value of .025 was considered significant because we performed two post hoc tests. Pearson's product–moment correlations were used to examine the relationship between HP variability measures of interest and treatment effects. For those subjects that had data before and after placebo treatment, the HP variability measures were compared using ANOVAs for repeated measures.

Results

Age was very similar between paroxetine and nortriptyline groups. There were no significant group differences between baseline and after-placebo lead-in periods for any of the HP variables. In fact, some of the values were almost identical. Tables 1 and 2 show the results of spectral analysis and measures of symbolic dynamics. Tables 3 and 4 show the results of two-way ANOVAs for the same measures.

For the two-way ANOVAs, drug effect refers to paroxetine versus nortriptyline and treatment effect for pre- versus posttreatment conditions. There were significant interaction and treatment effects for the mean 20-hour HP, significant interaction effect for the awake mean HP, and an interaction effect for the sleep mean HP (Tables 1 and 3; Figure 1). This was due to a significant decrease of R–R interval after nortriptyline treatment.

Spectral Measures

Tables 1 and 3 show the results of the spectral analyses. Two-way ANOVA of the 20-hour data showed no significant differences for TP, ULF, VLF, LF, or HF; however, there was a treatment effect for the LF/HF ratios, showing a significant decrease for both treatment conditions. There was also a significant increase of relative HF power during either condition as showed by the treatment effect (paroxetine: 2.1 ± 4.2 vs. 2.7 ± 4.6; nortriptyline: 1.3 ± 4.6 vs. 2.1 ± 2.0).

For the awake condition, there were significant interaction and treatment effects for TP, due to the decrease of TP during nortriptyline condition (Figure 2). For VLF, there were significant interaction and treatment effects suggesting a significant decrease during nortriptyline treatment (Figure 2). For LF, there also were significant interaction effects suggesting a significant decrease during nortriptyline treatment (Figure 2). For HF power, there was only a decrease during nortriptyline condition. There was a significant treatment effect for the LF/HF ratios suggesting a decrease during both treatments. There was also a significant increase of relative HF power during both treatments (paroxetine: 3.1 ± 4.8 vs. 4.1 ± 5.8; nortriptyline: 2.1 ± 1.4 vs 3.2 ± 2.8).

For the sleeping condition, there were significant interaction and treatment effects for TP, due to the decrease of TP during nortriptyline condition. For ULF, there was a significant treatment effect suggesting a decrease during either treatment condition; however, post hoc tests showed a significant decrease of ULF only for the nortriptyline condition. For VLF, there were significant interaction and treatment effects suggesting a significant decrease during nortriptyline treatment. For LF, there also were significant interaction and treatment effects suggesting a significant decrease during nortriptyline treatment.

Symbolic Dynamics

Tables 2 and 4 show the results of analysis using symbolic dynamics measures. Analysis of the 20-hour data revealed significant interaction effects for PN-5-A and PN-5-B suggesting an increase of the former measure and a

Table 1. Spectral Variables of Heart Period before and after Treatment

	Paroxetine		Nortriptyline	
	Predrug	Postdrug	Predrug	Postdrug
20 Hour				
Mean HP	865.23 ± 109.23	868.67 ± 123.80	843.50 ± 166.42	736.22 ± 132.41[c]
HP SD	119.08 ± 42.23	107.85 ± 32.12	122.86 ± 74.09	97.29 ± 29.94
TP	8.96 ± .85	8.78 ± .64	8.95 ± 1.04	8.39 ± .79
ULF	8.90 ± 1.27	8.55 ± .71	8.78 ± 1.10	8.25 ± .79
VLF	6.70 ± .64	6.62 ± .58	6.49 ± .68	5.87 ± .88
LF	5.38 ± .79	5.33 ± .63	5.23 ± .68	4.65 ± 1.00
HF	4.45 ± 1.13	4.59 ± .94	4.36 ± .86	4.10 ± 1.08
LF/HF ratio	3.57 ± 3.22	2.43 ± 1.30	3.03 ± 2.25	2.50 ± 2.33[a]
Awake				
Mean HP	816.49 ± 125.43	836.99 ± 108.53	800.61 ± 121.63	749.39 ± 109.83[a]
HP SD	80.48 ± 31.96	77.41 ± 18.68	89.31 ± 49.40	63.87 ± 23.68
TP	7.94 ± .76	7.95 ± .48	8.02 ± .91	7.51 ± .66[b]
ULF	7.59 ± .90	7.59 ± .53	7.73 ± 1.01	7.26 ± .71
VLF	5.99 ± .61	6.17 ± .60	5.95 ± .67	5.24 ± .89[c]
LF	4.91 ± .87	5.02 ± .68	4.89 ± .77	4.22 ± 1.13[c]
HF	3.99 ± .97	4.24 ± 1.01	3.98 ± .89	3.73 ± 1.02
LF/HF ratio	3.63 ± 3.59	2.70 ± 1.53	3.20 ± 2.35	2.25 ± 1.94[c]
Sleeping				
Mean HP	950.52 ± 103.76	973.63 ± 148.86	949.93 ± 209.11	850.75 ± 135.08[a]
HP SD	85.46 ± 28.72	77.51 ± 20.87	85.71 ± 32.53	59.69 ± 23.18
TP	8.08 ± .71	7.94 ± .56	8.09 ± .71	7.36 ± .70[c]
ULF	7.55 ± .82	7.29 ± .63	7.52 ± .81	6.87 ± .75[a]
VLF	6.60 ± .76	6.68 ± .65	6.64 ± .66	5.70 ± .97[c]
LF	5.40 ± .96	5.45 ± .73	5.64 ± .81	4.55 ± 1.10[b]
HF	4.54 ± 1.29	4.56 ± 1.05	4.60 ± 1.08	4.03 ± 1.17
LF/HF ratio	3.02 ± 2.29	3.12 ± 2.82	3.79 ± 3.14	2.51 ± 2.31

Total power (TP): 0–.5 Hz; ultra low frequency power (ULF): 0–.0033 Hz; very low frequency power (VLF): .0033–.04 Hz; low-frequency power (LF): .04–.15 Hz; high-frequency power (HF): .15–.5 Hz. The units for power are in Ln of milliseconds squared. HP, heart period. Significance indicates change from predrug condition in a paired *t* test (two-tailed).

[a] $p < .05$.
[b] $p < .01$.
[c] $p < .005$.

decrease of the latter during nortriptyline condition. For the awake condition, there was a significant interaction effect for word count (WC-100) during paroxetine condition as suggested by a significant interaction effect (Figure 3). There were significant interaction effects for PN-5-A and PN-5-B suggesting an increase of the former measure and a decrease of the later during nortriptyline condition. There was also a significant interaction effect for PN-100-A suggesting an increase of this measure only during nortriptyline condition (Figure 2).

For the sleeping condition, there was a significant interaction effect for PN-5-B suggesting a decrease during nortriptyline condition.

Fractal Dimension

There were no significant differences in FD for any of the periods for pre- and postdrug conditions (paroxetine: 20 hours: 1.23 ± .07 vs. 1.23 ± .07; awake: 1.24 ± .07 vs. 1.26 ± .08; sleeping: 1.29 ± .10 versus 1.28 ± .09; nortriptyline: 20 hours: 1.22 ± .04 vs. 1.20 ± .05; awake: 1.22 ± .05 versus 1.22 ± .05; sleeping: 1.27 ± .06 versus 1.25 ± .07).

Discussion

Spectral Analysis

The results clearly show that in these patients with depression and ischemic heart disease (mean age = 60 years), nortriptyline significantly decreases TP, ULF, VLF, and LF powers during awake and sleeping periods. Surprisingly, the effect of nortriptyline on HF power is not highly pronounced except during the awake state, and paroxetine did not result in any decrease in spectral powers. This is in contrast to the reports of Yeragani et al on paroxetine's effect on HF power in patients with panic disorder (Yeragani et al 1999); however, that study included patients with panic disorder without cardiac disease, and the mean age group of the patients was about 38 years. One other important finding in this study was the

Table 2. Symbolic Dynamic Measures of Heart Period before and after Treatment

	Paroxetine		Nortriptyline	
	Predrug	Postdrug	Predrug	Postdrug
20 Hour				
WSDVAR	1.99 ± .45	1.89 ± .41	2.02 ± .32	1.82 ± .33
Word Count	36.82 ± 6.38	38.88 ± 5.66	37.75 ± 5.18	37.63 ± 6.39
PN-5-A	52.72 ± 10.58	50.46 ± 10.56	53.19 ± 7.44	58.49 ± 10.98[a]
PN-5-B	5.95 ± 2.74	6.20 ± 2.68	5.25 ± 2.22	3.92 ± 3.17[a]
PN-100-A	98.91 ± 2.93	99.04 ± 2.75	99.56 ± .95	99.73 ± .45
PN-100-B	.004 ± .02	.032 ± .03	.002 ± .008	.0000 ± .0000
Awake				
WSDVAR	1.62 ± .51	1.59 ± .44	1.65 ± .48	1.39 ± .40
Word Count	32.21 ± 6.09	35.00 ± 6.00[b]	33.70 ± 6.02	33.2 ± 5.86
PN-5-A	53.57 ± 12.49	50.26 ± 12.15	54.48 ± 9.83	59.26 ± 11.08
PN-5-B	4.68 ± 3.23	5.32 ± 2.92	3.98 ± 2.10	3.24 ± 3.08
PN-100-A	99.50 ± 1.70	99.42 ± 1.60	99.72 ± .57	99.83 ± .38
PN-100-B	.0004 ± .002	.0008 ± .003	.0005 ± .002	.0000 ± .0003
Sleeping				
WSDVAR	1.39 ± .36	1.26 ± .43	1.27 ± .36	1.13 ± .59
Word Count	30.88 ± 7.27	30.82 ± 6.94	31.00 ± 4.61	29.07 ± 6.81
PN-5-A	49.54 ± 10.22	50.24 ± 9.81	49.34 ± 8.64	55.03 ± 10.89
PN-5-B	6.81 ± 3.77	7.64 ± 4.17	7.90 ± 2.69	4.74 ± 3.13[a]
PN-100-A	98.45 ± 4.23	98.71 ± 4.26	99.26 ± 1.81	99.75 ± .55
PN-100-B	.009 ± .04	.008 ± .03	.007 ± .03	.0000 ± .0000

WSDVAR, standard deviation of the word sequence; PN, percentage of three digit words (000 or 111) for a given period (5 to 100 milliseconds). Significance indicates change from predrug condition in a paired *t* test (two-tailed).
[a] $p < .05$.
[b] $p < .005$.

decrease of sleep ULF power with nortriptyline, which is especially important in light of the report of Bigger et al (1992) linking the decrease in ULF power to significantly increased mortality in cardiac patients. There was a significant decrease of LF/HF ratios during both treatments, but it was more pronounced during the nortriptyline condition, which may in fact be a beneficial effect. The concept of LF/HF ratio as a relevant measure of sympathovagal balance is controversial, however (Cacioppo et al 1994; Pagani et al 1986) and this finding should also be viewed in the total context of a decrease in HP variability in various frequency bands. As expected, there was a significant decrease of mean HP during nortriptyline treatment. The increase in relative HF power during either

Table 3. Results of Two-Way Analysis of Variance for Spectral Variables of Heart Period before and after Treatment

	Group effect	Treatment effect	Interaction effect
20 Hour			
Mean HP	*ns*	$F = 6.3$; $df = 1,31$; $p = .02$	$F = 7.6$; $df = 1,31$; $p = .009$
LF/HF Ratio	*ns*	$F = 5.7$; $df = 1,31$; $p = .02$	*ns*
Awake			
Mean HP	*ns*	*ns*	$F = 5.6$; $df = 1,42$; $p = .02$
TP	*ns*	$F = 5$; $df = 1,42$; $p = .03$	$F = 5.2$; $df = 1,42$; $p = .03$
VLF	ns	$F = 8.3$; $df = 1,42$; $p = .006$	$F = 22.8$; $df = 1,42$; $p = .00001$
LF	*ns*	$F = 6.2$; $df = 1,42$; $p = .05$	$F = 12.4$; $df = 1,42$; $p = .001$
HF	*ns*	*ns*	$F = 4.0$; $df = 1,42$; $p = .05$
LF/HF Ratio	*ns*	$F = 7.0$; $df = 1,42$; $p = .008$	*ns*
Sleep			
Mean HP	*ns*	*ns*	$F = 7.9$; $df = 1,28$; $p = .009$
TP	*ns*	$F = 13.7$; $df = 1,28$; $p = .0009$	$F = 6.1$; $df = 1,28$; $p = .02$
ULF	*ns*	$F = 6.0$; $df = 1,28$; $p = .02$	*ns*
VLF	*ns*	$F = 13.8$; $df = 1,28$; $p = .0009$	$F = 18.9$; $df = 1,28$; $p = .0001$
LF	*ns*	$F = 13.6$; $df = 1,28$; $p = .001$	$F = 16.3$; $df = 1,28$; $p = .0004$

Total power (TP): 0–.5 Hz; ultra low frequency power (ULF): 0–.0033 Hz, very low frequency power (VLF): .0033–.04 Hz, low-frequency power (LF): .04–.15 Hz, high-frequency power (HF): .15–.5 Hz. The units for power are in Ln of milliseconds squared. HP, heart period.

Table 4. Results of Two-Way Analysis of Variance for Measures of Symbolic Dynamics of Heart Period before and after Treatment

	Group effect	Treatment effect	Interaction effect
20 Hour	*ns*	*ns*	
PN-5-A	*ns*	*ns*	$F = 6.2$; $df = 1,13$; $p = .02$
PN-5-B	*ns*	*ns*	$F = 4.4$; $df = 1,31$; $p = .04$
Awake			
WC-100	*ns*	*ns*	$F = 5.0$; $df = 1,42$; $p = .03$
PN-5-A	*ns*	*ns*	$F = 6.2$; $df = 1,42$; $p = .03$
PN-5-B	*ns*	*ns*	$F = 4.3$; $df = 1,42$; $p = .04$
PN-100-A	*ns*	*ns*	$F = 4$; $df = 1,42$; $p = .05$
Sleeping			
PN-5-B	*ns*	*ns*	$F = 9.3$; $df = 1,28$; $p = .005$

PN, percentage of three digit words (000 or 111) for a given period (5 to 100 milliseconds); WC, word count.

treatment condition is most likely due to a more significant decrease in total power compared with HF power. This again underscores the importance of using absolute as well as relative powers. It also explains, in part, the significant decrease of LF/HF ratios during both drug conditions.

Paroxetine and Antimuscarinic Effects

A brief review of the literature suggests that, compared with tricyclics, paroxetine has weak affinity for muscarinic receptors (e.g., 15-fold weaker than amitriptyline; Johnson 1989; Thomas et al 1987). Hiemke (1994) stated that the low affinity of paroxetine to muscarinic receptors is not relevant for therapeutic effects because paroxetine is 2 to 23 times more potent for the reuptake inhibition of serotonin than other SSRIs. Hunter and Wilson (1995) reported that tricyclics produced a significant reduction in salivary flow, presumably due to muscarinic receptor blockade. Fluoxetine and paroxetine did not produce any

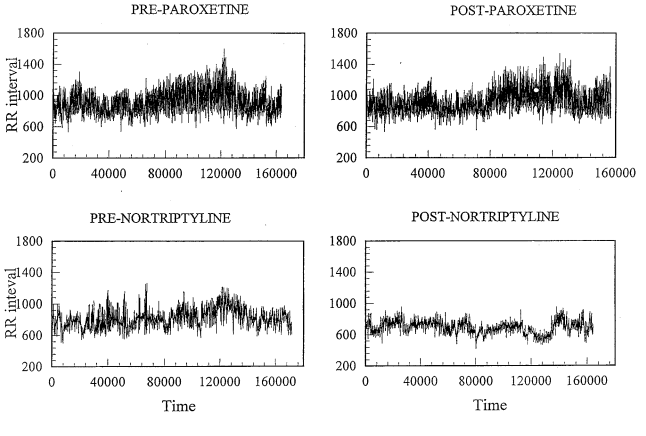

Figure 1. The 24-hour heart period time series for one patient in each drug condition. RR, interbeat interval in milliseconds.

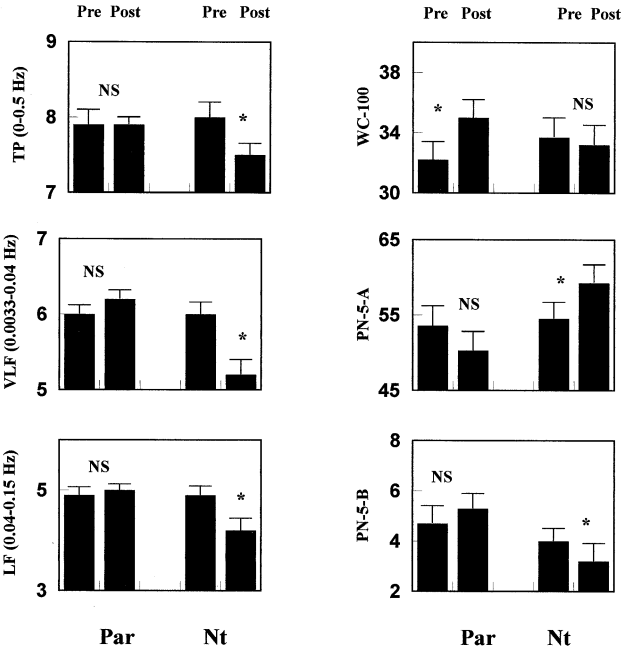

Figure 2. Interaction effects (analysis of variance) for the paroxetine and nortriptyline conditions. Significant differences are for pre- versus postdrug. TP, total power; VLF, very low frequency; LF, low frequency; WC, word count; PN, percentage of three digit words (000 or 111) for a given period (5 to 100 milliseconds); Par, paroxetine; Nt, nortriptyline.

significant change in this variable. Pollock et al (1998) also reported that at therapeutic plasma concentrations, paroxetine is associated with approximately one fifth the anticholinergic potential of nortriptyline in older patients. Bitsios et al (1999) studied the effects of venlafaxine, paroxetine, and desipramine on the pupillary light reflex in

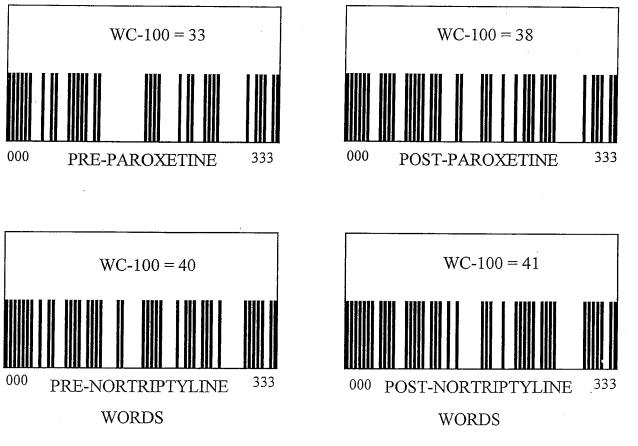

Figure 3. The 20,000-sec awake word count (WC-100) for a patient after nortriptyline treatment and another after paroxetine treatment condition, illustrating increased word count after paroxetine treatment.

humans and found no significant changes with paroxetine, whereas venlafaxine was associated with significant increase in resting pupil diameter and a decrease in amplitude. They concluded that this is consistent with blockage of noradrenaline uptake. Owens et al's study (Owens et al 1997) also suggests that paroxetine does not have significant affinity for Muscatine receptors. These studies support a lack of significant antimuscarinic effects of paroxetine.

For spectral analysis, the results of awake and sleeping periods showed highly significant differences compared with the 20-hour period, most likely attributable to an increased variance of each measure when longer data segments, especially the combination of awake and sleeping periods, were used.

Symbolic Dynamics

There was a significant increase in PN-5-A during the 20-hour and awake periods and a decrease of PN-5-B during 20-hour as well as awake and sleeping periods after nortriptyline due to a decreased complexity of the time series. This means that many consecutive differences in R–R intervals after nortriptyline that occur in a row are $<$ 5 msec. This is because PN-5-A indicates the occurrence of $<$ 5 msec consecutive differences in the R–R interval time series, whereas PN-5-B indicates the occurrence of $>$ 5-msec consecutive differences in the R–R intervals. It is interesting to note that word count significantly increased after paroxetine administration during the awake period. This is important in connection with our previous findings of decreased number of words in patients with panic disorder, which suggests a decreased nonlinear complexity of the time series (Yeragani et al 2000a). Similar findings were also reported in patients with cardiac disease (Voss et al 1996).

Fractal Dimension

Fractal dimension calculated by the technique described by Katz (1988) correlates highly significantly with the HF power of HR or HP time series and also the APEN values calculated using the technique of Pincus et al (Pincus et al (1991) (Yeragami et al 1993b, 1997, 1998b). Thus, it is not surprising that there were no consistent and significant changes in this measure in our study because the significant findings were mostly limited to ULF, VLF, and LF bands for the nortriptyline condition.

As we described in our previous reports (Radhakrishna and Yeragani, 2001; Yeragani et al 2000a), we did not find robust correlations between some of the nonlinear measures, such as WC-100 and LLE, and the spectral measures. Also, these measures discriminated normal control subjects from patients with panic disorder more effectively and also appear to be useful additions to measures of time and frequency domain.

Cardiac Autonomic Function and Cardiovascular Mortality

Cole et al (1999) recently showed that exercise recovery time is prolonged in people who are prone to significant cardiovascular events, which again relates impaired cardiac vagal function to an increased risk for cardiovascular mortality. Carney et al (2000) showed an improvement in the parameters of HRV in depressed patients with myocardial infarction who underwent cognitive psychotherapy. Thus, the effectiveness of various treatment approaches should be evaluated in the context of cardiovascular effects and probably using some of the newer nonlinear measures such as the ones used in this study. Other measures, including measures of chaos, may prove effective in identifying other subtle changes in autonomic function. Pool (1989) suggested that the condition of health is in fact associated with a higher degree of chaos.

Conclusions

The findings of this study suggest a more profound vagolytic function of nortriptyline in patients with major depression and cardiac disease. Thus, paroxetine may be a safer choice in patients with myocardial infarction, perhaps because of its weaker antimuscarinic effects. Each case should be treated on its own merit, and, when possible, some of the noninvasive measures described here should be obtained before and after treatment.

Limitations of our study include the fact that we had to exclude people in the placebo group (after placebo lead in), leaving us with fewer subjects for comparison; however, the values of various HRV measures were similar, and there were no significant differences between these two pre- and postplacebo periods. The measures of symbolic dynamics are relatively new, and future studies are needed to understand the exact nature and utility of these measures.

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Appendix 1. Calculation of Fractal Dimension and Symbolic Dynamic Measures

Fractal Dimension (FD) was calculated according to the same method used in our previous studies (Yeragami et al 1993b, 1997), which was originally described by Katz (1988):

$$D = \log (L/a)/\log[(K/a)/A],$$

where D is the fractal dimension, L is the total length of the curve, a the average step length ($a = L/n$, where n is the total number of steps), $K = 2/\pi$, and A is the area of the circle potentially filled by an ideal random walk. The following can be obtained after removing the constant K from the formula:

$$D = \log(n)/\log(nd/L) = \log(n)/[\log(n) + \log(d/L)]$$

where L is the sum of distances between successive points, d is the planar extent of the curve that is the farthest distance between starting point and the ith point of the time series, and n is the number of steps in the curve.

Thus, the FD of a planar curve is defined as

$$FD = \log (L)/\log(d),$$

where L is the total length of the curve and d is the diameter or planar extent of the curve. As suggested by Katz (1998), we adopted the formula

$$FD = log(L/a)/log(d/a) = log(n)/[log(n) + log(d/L)],$$

where n is the total number of steps in the curve (total number of points − 1) and a is the average distance between successive points. We used the same method suggested by Katz (1988) using a custom-developed software program. We calculated FDs for the 20-hour data and also the awake and sleeping periods (20,000 sec each).

Symbolic Dynamics

These techniques have been described in detail by Kurths et al (1995) and Voss et al (1996) and were recently used in our study of patients with panic disorder (Yeragani et al 2000a). These techniques use a coarse-graining technique, and the time series of the HP are transformed into symbol sequences, such as 000, 011, 022, 033 . . . up to 333 by using 0, 1, 2, and 3 as the symbols. For these four symbols, there are 64 three-symbol sequences or "words," which are basically three-digit sequences. The transformation is done using the mean R–R interval as μ and a as a special parameter, which is set to 0.05 to 0.1. Voss et al (1996) reported that any value between 0.05 and 0.1 would give reliable results for the R–R interval time series. In our previous study, we called these parameters for total word count WC-50 and WC-100 (to indicate the value of a as 0.05 or 0.1, respectively) and found that the values were highly correlated. In this study, we present only WC-100 values for the word count.

The transformation for 0, 1, 2, and 3 is done in the following way:

$$\mu < tn - tn - 1 \leq (1 + a) \times \mu \quad (0)$$

$$(1 + a) \times \mu < t_n - t_n - 1 < \infty \quad (1)$$

$$(1 - a) \times \mu < t_n - t_n - 1 \leq \mu \quad (2)$$

$$0 < t_n - t_n - 1 \leq (1 - a) \times \mu \quad (3)$$

Here $< tn - tn - 1$ indicates the R–R interval, μ, the mean of the R–R interval and a the parameter set at 0.1. Thus, for each R–R interval, one symbol is assigned, and for n number of intervals, $n - 1$ words (three-digit symbols) are obtained.

We have also calculated the SD of the word sequence (WSDVAR-100) after transformation of the sequence by using the words 1 or 3 as suggested by Voss et al (1996). In another analysis, we obtained the symbol sequences using only 0 or 1 where 0 represents the difference between consecutive beats lower than 5, or 100 msec and 1 the cases in which the difference between two successive beats exceeded this limit. Then we calculated all three-digit words that contained either 000 (A) or 111 (B). We call these PN-5-A, PN-100-A and PN-5-B, and PN-100-B, respectively.