Altered Heart Rate Variability in Panic Disorder Patients

Ehud Klein, Elena Cnaani, Tamar Harel, Simon Braun, and Shlomo A. Ben-Haim

Resting electrocardiographic recordings were obtained from 10 patients with panic disorder (PD) and 14 normal controls. Signal analysis of the beat-to-beat heart rate variability was performed by means of power spectrum analysis. The analysis revealed that patients with PD had marked reduction in the high-frequency peaks of the power spectrum densities. An Energy Ratio Index (ERI), which accurately differentiated between patients and controls, was calculated. In PD patients, a significant correlation was demonstrated between the clinical ratings and the energy ratios. Our findings suggest that decreased heart rate variability may be a characteristic of PD. The importance of this finding as a diagnostic marker and the underlying pathophysiological mechanisms need to be further explored.

Key Words: Panic disorder, signal analysis, heart rate variability, power spectrum

Introduction

Alarming somatic symptoms, and cardiovascular symptoms in particular, are among the hallmarks of panic attacks, along with the intense fear of dying and loss of control which are so often described by many patients (American Psychiatric Association, 1987). The temporal relationship between somatic symptoms and the initiation of panic attacks is not clear; Some believe that somatic symptoms are the result of a primary event at the level of the central nervous system (CNS) (Klein et al 1981; Carr and Sheehan 1984; Charney et al 1984); others suggest that increased awareness and sensitivity to somatic events play a key role in triggering panic attacks (Hibbert 1984; Clark 1986). Either way, the autonomic nervous systems seems to be intimately involved in the initiation and manifestation of panic attacks.

From the Department of Psychiatry, Rambam Medical Center (EK, EC); the Cardiovascular Research Group, Rappaport Family Institute for Research in the Medical Sciences (TH, SAB-H); the Bruce Rappaport Faculty of Medicine (EK, SAB-H); and the Faculty of Mechanical Engineering (SB), Technion-Israel Institute of Technology, Haifa, Israel.

Address reprint requests to Ehud Klein, M.D., Department of Psychiatry, Rambam Medical Center, P.O.B. 9602, 31096 Haifa, Israel, fax: 972-4-510941.

Received January 12, 1993; revised April 4, 1994.

Patients with panic disorder (PD) have higher baseline heart rate (HR) (Nesse et al 1984; Liebowitz et al 1985) and periods of tachycardia which coincide with panic symptoms (Taylor et al 1982/3; Freedman et al 1985). No electrocardiographic (ECG) abnormalities have been characterized in these patients; however, increased cardiac mortality and morbidity have been suggested (Coryell et al 1986, 1989).

Although HR variability was documented more than 200 years ago, its mechanism was only recently described (Akselrod et al 1981). HR variability has been found to be the outcome of rapidly reacting cardiovascular control systems, namely, the sympathetic and parasympathetic branches of the autonomic nervous system (Pagani et al 1986; Saul 1990).

Over the last several years, power spectrum analysis has been utilized to quantify spontaneous HR variability in humans (Saul 1990). This technique has provided, by the analysis of simple noninvasive ECG recordings, valuable information about factors that control HR (Akselrod 1981, 1985). The frequencies in the power spectrum that are contributed by the various factors controlling HR, primarily the autonomic nervous system, have been characterized (Ak-

0006-3223/95/$09.50
SSDI 0006-3223(94)00130-U

selrod et al 1985). It has been shown that the higher-frequency peaks of the power spectrum reflect parasympathetic activity, while the lower-frequency peaks reflect predominantly sympathetic activity (Akselrod et al 1985; Saul 1990).

In the present study we utilized power spectrum analysis of the beat-to-beat variation in ECG recordings obtained from PD patients and normal controls to characterize HR variability and possible alterations in autonomic neural output to the heart in PD patients during resting conditions.

Methods

Patients who were referred to the anxiety disorder clinic at our medical center were considered eligible for this study if they satisfied DSM-III-R criteria (American Psychiatric Association 1987) for PD with or without agoraphobia. Ten patients with PD (four males, six females; mean age 32 ± 6.7 years) gave informed consent to participate in the study. ECG recordings were obtained after the patients had been drug-free for 2 weeks. Seven of the patients had a second recording after remission of symptoms following drug treatment. Clinical ratings were obtained, before and after treatment, by the Hamilton Depression Rating Scale (HDRS) total score and anxiety subscore (Hamilton 1960) and a Panic Attack Inventory.

The control group was comprised of 14 healthy volunteers (four males, 10 females; mean age 32 ± 7.2 years) with no history of psychiatric disorder. ECG recordings were obtained from these volunteers under conditions identical to those for the PD patients. Both patients and controls were comparable in their degree of physical fitness. None of the subjects was involved in intense regular physical activity, and all considered themselves as average with regard to physical fitness.

ECG Recording

All subjects were invited to the laboratory, where the recordings were taken between 9.30 AM and 12.30 AM. Subjects were placed on a comfortable bed and connected to a conventional ECG amplifier and FM tape recorder. To minimize anticipatory anxiety, a pleasant atmosphere was kept and a detailed explanation of the procedure was made. After 10 minutes allowed for stabilization, the ECG was continuously recorded for 5–10 minutes. All recordings were done in the supine position during complete rest.

Data Analysis

Off-line analysis was performed on a personal microcomputer. ECG data were played back from the FM tape and digitized at 1 kHz with 12-bit resolution. The computer program automatically derives coefficients necessary to define the power spectrum density (PSD) estimate. The details of this procedure have been described elsewhere (Pagani et al 1986).

An index describing the ratio between the PSD of frequencies between 0 and 0.2 cycles/beat (low frequencies) to that of frequencies between 0.2 and 0.5 cycles/beat (high frequencies) was calculated for each case. The cutoff of 0.2 cycles/beat was derived from previous studies that analyzed quantitatively the PSD in relation to sympathovagal control of the cardiovascular functions (Pagani et al 1986; Saul 1990). This index was used to compare PD patients to normal controls and was termed the Energy Ratio Index (ERI).

We evaluated the correlations between the energy ratios and the clinical ratings to assess whether the energy ratios of the power spectra of the HRV are able not only to differentiate between PD patients and control subject, but also might reflect the severity of the clinical condition in the patients. For this calculation, the computer program automatically searched for the cutoff frequency that yielded the highest correlation between this energy ratio and the clinical ratings. Obviously, control subjects could not be included in this analysis, since their clinical ratings were uniformly low.

Statistics

The Mann-Whitney Rank Sum Test was used to examine statistical significance of the difference in ERI between the two groups, and also to examine the difference in the high-frequency peak (area under the curve, or AUC) between the two groups. Fisher test with HR as a covariate was used to assess the effect of HR on the difference between the two groups.

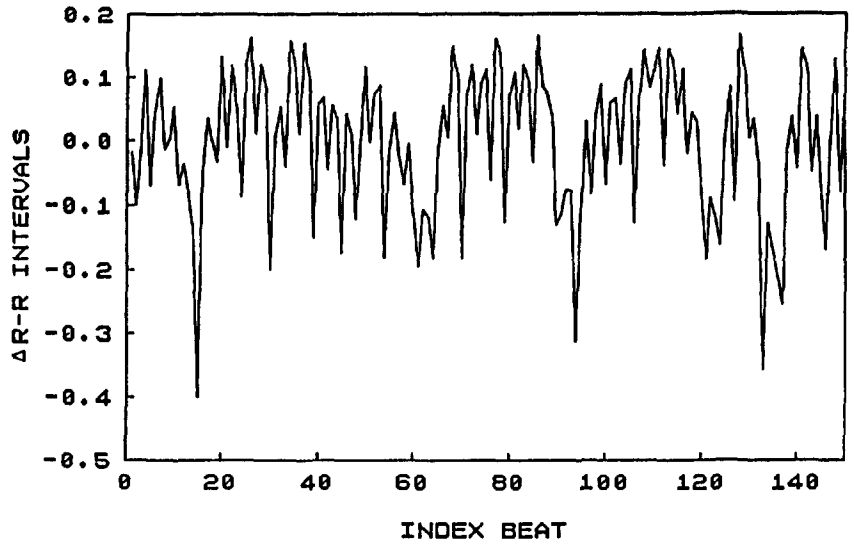
Spearman Rank Correlation coefficients were calculated to examine if there was a correlation between heart rate and the ERI. Correlation coefficients were also calculated between the ERIs of individual patients and the scores of the given clinical rating scales. The correlation was considered significant when a p value smaller than 0.05 was observed.

Nonparametric statistical tests were used because of the small sample size, which precluded an assumption of normal distribution of the results, and the fact that nonordinal scales were used.

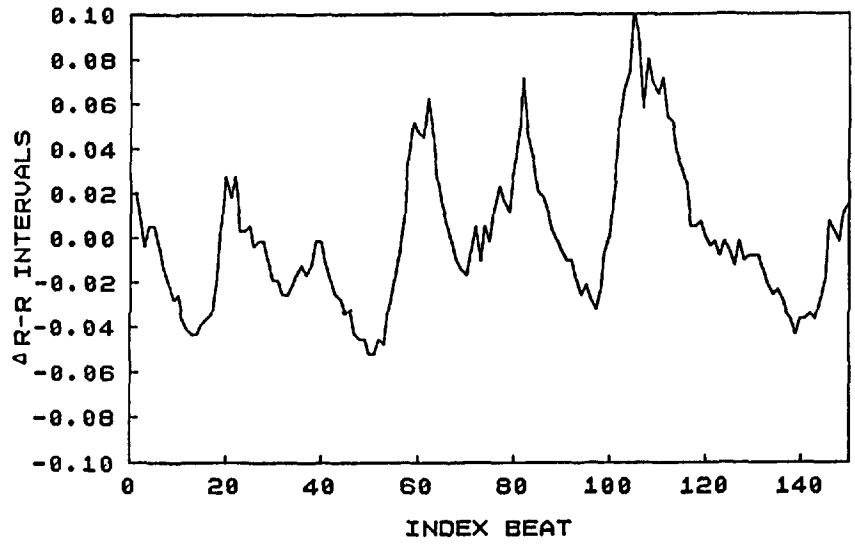
Accuracy, specificity, and sensitivity were computed for the ERI, to test its capability to distinguish PD patients from normal subjects.

Results

The tachograms and the PSDs of PD patients were markedly different from those of the control subjects. Figure 1 depicts a typical normalized tachogram with the mean cardiac interval subtracted (R-R variability) of a normal subject (Figure 1a) and a PD patient (Figure 1b). It is evident from the figure that high-frequency oscillations present in the R-R variabi-



(a)



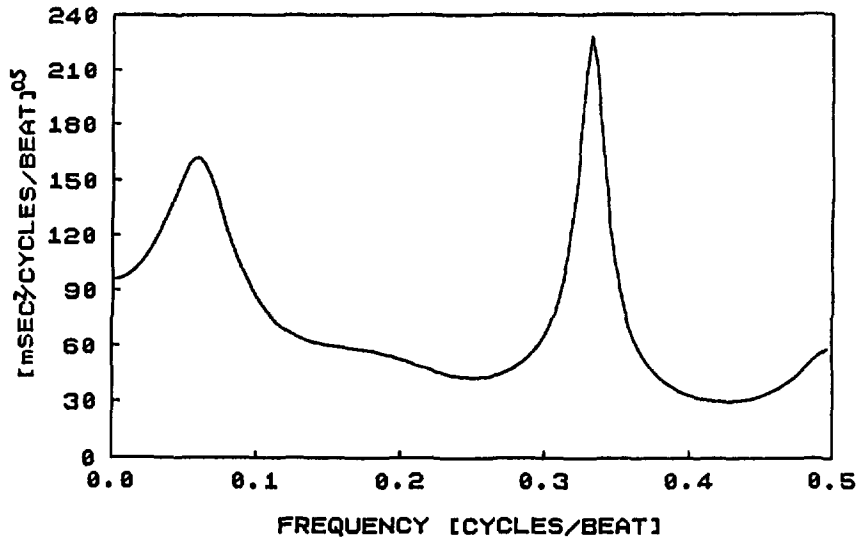
(b)

Figure 1. Typical normalized tachogram with the mean cardiac interval subtracted (R-R variability) of: (a), a normal subject, (b), a panic disorder (PD) patient. (The high-frequency oscillations present in the R-R variability signal of normal subjects are not present in the PD patient.)

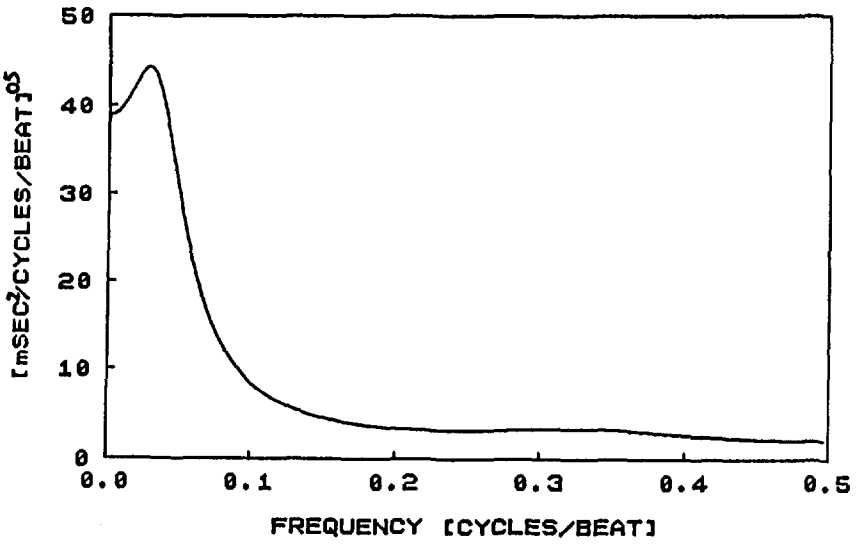
lity signal of the normal subject are not present in the PD patient. These differences were seen most easily in the typical PSD of a normal subject (Figure 2a) and that of a PD patient (Figure 2b). It is evident from the figure that the high-frequency component (> .2 cycles/beat) was markedly attenuated in the PD patient.

PD patients had significantly higher HR than normal subjects: 93 ± 22 versus 71 ± 7 beats/minute ($p < .005$).

The mean value for the ERI was significantly higher in the PD patients (3.32 ± 0.12) than in the normal subjects (1.91 ± 0.86) ($p < .05$) (Figure 3). To assess the relationship between the difference in HR of the two groups and the difference in the ERI, we compared the two groups using HR as a covariate. The results indicated that HR could not account for the difference, which remained significant ($F = 5.86$; $p < .025$). We also correlated HR to the ERI in the patients and control subjects; in either case, no significant correlation was demonstrated ($r = .24, p = .5$ and $r = .26, p =$



(a)



(b)

Figure 2. Typical power spectrum density of: (a), a normal subject, and (b), a panic disorder patient. Note the significant diminution of the high-frequency content (> .02 cycles/beat).

37, respectively). Using a threshold of 2.82 for the ERI, PD patients could be separated from normal subjects with an accuracy of 83.3% (specificity of 92.86% and sensitivity of 70%) (Figure 3).

Since the major change in the PD patients was seen in the high-frequency component, we also compared the high-frequency peak between patients and controls. Thus, we compared the estimated power spectra of the frequencies higher than 0.2 cycles/beat. The mean AUC of the high-frequency peaks was found to be significantly lower in PD patients (0.25 + 0.09) compared to control subjects (0.36 ± 0.11 ($p < .008$ Mann-Whitney).

A statistically significant positive correlation was found between the energy ratios and the HDRS, the HDRS anxiety subscore, and the number of panic attacks ($r = .67, p < .05$; $r = .77, p < .02$; and $r = .65, p < .05$, respectively).

Seven patients were recorded a second time after clinical improvement on medications (four on alprazolam and three on imipramine). Clinically, these patients had a significant reduction in the number of panic attacks following treatment (from 5.7 ± 4.4 to 0.7 ± 0.9; $p < .05$). ERI values in these patients declined following treatment and were not significantly different from those of controls subjects (2.41 ± 0.82 vs. 1.91 ± 0.86; NS).

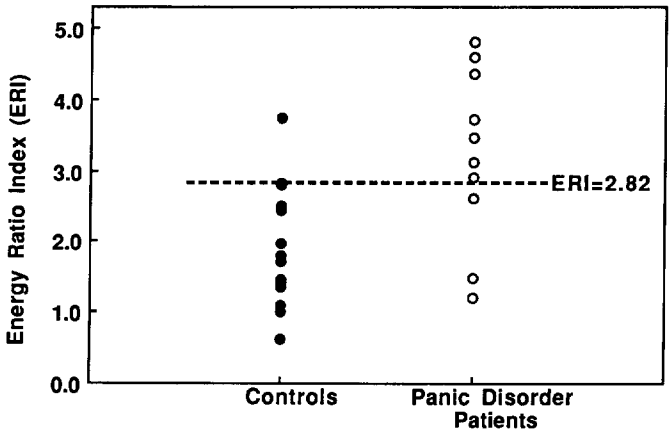


Figure 3. Distribution of Energy Ratio Index (ERI) among panic disorder (PD) patients and controls. A threshold of 2.82 most accurately distinguished between PD patients and normal subjects (accuracy, 83.3%; specificity, 92.86%; sensitivity, 70%).

Discussion

Using signal analysis of ECG recordings we have demonstrated altered HR variability and reduction of the high-frequency components of the PSD in PD patients compared to normal controls. This reduction in high-frequency components of the PSD was expressed by a change in magnitude of the ERI (derived from the ratio of low- and high-frequency bands of the PSD at a cutoff frequency of 0.2 cycles/beat), which yielded significantly higher values for PD patients compared to control subjects. An accurate discrimination between patients and controls was achieved by setting a threshold of 2.82 for the ERI (accuracy 83.3%, specificity 92.86%, sensitivity 70%). However, our sample size is too small to consider this as a sensitive marker for PD. The difference between the two groups was also significant when the high-frequency peaks of the power spectra (> 0.2 cycles/beat) were compared, reflecting the absolute decrease in the high-frequency component in PD patients.

The usefulness of this approach using signal analysis of ECG recordings recently has been demonstrated also by others (Yeragani et al 1991, 1993). Similar to our findings, these authors reported decreased HRV in PD patients (Yeragani et al 1993), while depressed patients failed to show changes in HRV compared to normal controls (Yeragani et al 1991).

As previously demonstrated (Nesse et al 1984; Liebowitz et al 1985), PD patients in our sample also showed significantly higher HR than control subjects. However, in another study which reported autonomic function in PD patients, baseline mean HR was similar to that of the control group (Yeragani et al 1993). Thus, differences in heart rate *per se* do not seem to be reliable in differentiating the two groups. While there was no evidence of clinical anxiety during the recording, the increased HR could reflect a state of increased physiological arousal in our PD patients, which was due to subclinical anxiety. Thus, it is possible that the difference in the power spectra is a direct result of the difference in HR. To address this question, we performed additional analysis comparing the two groups with heart rate as a covariate. The difference in the ERI between the two groups remained significant, even when HR was accounted for. Furthermore, we have also shown that no significant correlation could be demonstrated between HR and the ERI in both PD and control patients. We thus think it can be stated confidently that the differences in the ERI of the two groups are not directly related to the differences in HR. This conclusion is further supported by a recently published study where similar findings were reported in the absence of differences in baseline HR during the recording (Yeragani et al 1993).

In the PD patients, significant correlations were observed between the energy ratios and the clinical ratings. These results indicate that utilizing the PSD method for HR variability signals might be useful, not only in the differentiation of PD patients from normal subjects but also for assessment of the severity of the clinical condition. However, more patients need to be studied in order to prove the usefulness of these markers.

Also of interest is the finding that in the seven patients who were recorded a second time, following remission of symptoms after pharmacotherapy as evidenced by the reduction in the number of panic attacks (four patients treated with alprazolam, three with imipramine), ERI values declined and were found to be not significantly different from those of control subjects. It could be suggested that this change under treatment is related to anticholinergic effects

of the medications used and not to their clinical effect. This is not very likely, since four of the patients received alprazolam, which lacks significant anticholinergic properties. Furthermore, the anticholinergic effect of imipramine should in fact work in the opposite direction—namely, further decrease in HRV, as has been demonstrated with atropine (Pfeifer et al 1982). This might indicate that the reduction in high-frequency components of the PSD and alterations in HR variability observed in our patients are state-dependent phenomena related to clinically active PD.

Only careful statements should be made at this point about the physiological significance of these findings. As mentioned before, the higher-frequency components of the PSD reflect parasympathetic activity. Our findings may thus suggest that in PD patients, resting cardiac activity is characterized by alterations in sympathovagal balance which result primarily from a reduction in parasympathetic tone.

It might be suggested that the ERI actually reflects the dynamic balance between the sympathetic and vagal branches of the autonomic cardiac innervation, and thus could be referred to as a sympathovagal control index. Traditionally, it has been postulated that increased noradrenergic activity in PD results in increased activity of the sympathetic nervous system (Ko et al 1983; Charney et al 1984; Villacres et al 1987). However, since the parasympathetic system modulates the activity of the sympathetic system on the heart via tonic inhibition (Berne and Levy 1986), reduction in parasympathetic tone could result in increased noradrenergic activity on the heart (Lundberg and Hokfelt 1983; Berne and Levy 1986). Furthermore, the increase in basal HR in PD patients, which has been shown in several other studies as well as ours, is more readily explained by a reduction in parasympathetic control; it has been shown that spontaneous resting HR increases by 50% following complete blockade of sympathetic and parasympathetic input (Berne and Levy 1986; Villacres et al 1987). This indicates that under normal conditions the parasympathetic system plays a more dominant role in determining HR.

A recently published study (George et al 1989) could support the possibility that the clinical manifestations of PD may be associated with a reduction in parasympathetic tone. In this study it was demonstrated that lactate infusion and hyperventilation substantially attenuate vagal tone in normal volunteers. Both procedures are known to provoke panic attacks in PD patients. Little work has been published about the role of the parasympathetic and central cholinergic system in anxiety in general and in PD in particular; these findings suggest that this area needs further investigation.

The question of the specificity of these findings to PD patients remains open at this point; however, some evidence supporting such a possibility comes from recent work of Yeragani et al (1991, 1993). As mentioned before, these researchers have shown similar results to ours with PD patients, but no changes in HR variability in patients with major depression.

Conclusion

In conclusion, we have shown in this study that signal analysis of simple ECG recordings may serve as a valuable marker for PD. These findings may provide a useful measure that could be of help in the diagnosis and follow-up of PD patients. To determine whether these findings are specific to PD or nonspecifically reflect states of increased anxiety and arousal, however, patients with other anxiety disorders such as generalized anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder, need to be studied.

References

Akselrod SD, Gordon D, Ubel AF, Shannon DC, Barger CA, Cohen RJ (1981): Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 213:220–222.

Akselrod SD, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ (1985): Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol* 249:H867–H875.

American Psychiatric Association (1987): *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed rev. Washington, DC: American Psychiatric Press.

Berne RM, Levy MN (1986): Regulation of the heart rate. In Berne RM, Levy MN (eds), *Cardiovascular Physiology.* St Louis: CV Mosby Co, pp 76–104.

Carr DB, Sheehan DV (1984): Panic anxiety: a new biological model. *J Clin Psychiatry* 45:323–330.

Charney DS, Heninger GR, Breier A (1984): Noradrenergic function in panic anxiety: effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 41:751–763.

Clark DM (1986): A cognitive approach to panic. *Behav Res Ther* 24:461–470.

Coryell W, Noyes R, House JD (1986): Mortality among outpatients with anxiety disorders. *Am J Psychiatry* 143:508–510.

Coryell W, Noyes R, Clancy J (1989): Excess mortality in panic disorder: a comparative study with primary unipolar depression. *Arch Gen Psychiatry* 46:701–703.

Freedman RR, Ianni P, Ettedgui E, Puthezhath N (1985): Ambulatory monitoring of panic disorder. *Arch Gen Psychiatry* 42:244–248.

George DT, Nutt DJ, Walker WV, Porges SW, Adinoff B, Linnoila M (1989): Lactate and hyperventilation substantially attenuate vagal tone in normal volunteers. *Arch Gen Psychiatry* 46:153–156.

Hamilton M (1960): A psychiatric rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56–62.

Hibbert GA (1984): Ideational components of anxiety: their origin and content. *Br J Psychiatry* 144:618–624.

Klein DF (1981): Anxiety reconceptualized. In Klein DF, Rahkin J (eds), *Anxiety: New Research and Changing Concepts*. New York: Raven Press, pp 235–263.

Ko GN, Elsworth JD, Roth RH, Rifkin BG, Leigh H, Redmond E (1983): Panic-induced elevation of plasma MHPG levels in phobic-anxious patients: effects of clonidine and imipramine. *Arch Gen Psychiatry* 40:425–430.

Liebowitz MR, Gorman JM, Fyer AJ, et al (1985): Lactate provocation of panic attacks. II. Biochemical and physiological findings. *Arch Gen Psychiatry* 42:709–719.

Lundberg JM, Hokfelt T (1983): Coexistence of peptides and classical neurotransmitters. *Trends Pharmacol Sci* 6:325–333.

Nesse RM, Cameron OG, Curtis GC, McCann DS, Huber-Smith MJ (1984): Adrenergic function in patients with panic anxiety. *Arch Gen Psychiatry* 41:771–776.

Pagani S, Lombardi, Guzetti S, et al (1986): Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. *Circ Res* 59:178–193.

Pfeifer MA, Cook D, Bradsky J, et al (1982): Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man. *Diabetes* 31:339–345.

Saul JP (1990): Beat-to-beat variations of heart rate reflect modulation of cardiac autonomic outflow. *News in Physiological Sciences* 5:32–37.

Taylor CB, Telch MJ, Havvik D (1982): Ambulatory heart rate changes during panic attacks. *J Psychiatr Res* 17:261–266.

Villacres EC, Hollifield M, Katon WJ, Wilkinson CW, Veith RC (1987): Sympathetic nervous system activation in panic disorder. *Psychiatry Res* 21:313–321.

Yeragani VK, Pohl R, Berger R, et al (1993): Decreased heart rate variability in panic disorder patients: A study of power-spectral analysis of heart rate. *Psychiatry Res* 46:89–103.

Yeragani VK, Pohl R, Balon R, et al (1991): Heart rate variability in patients with major depression. *Psychiatry Res* 37:35–46.