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Research report

Anxiety and autonomic regulation in major depressive disorder: an exploratory study

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Abstract

Spectral analysis of fluctuations in heart rate and blood pressure was employed to explore sympathetic and parasympathetic cardiovascular control mechanisms in relation to trait anxiety in major depressive disorder. Sixteen drug-free female depressed patients were divided into two groups: those who were high on trait anxiety (HTA, $n = 9$) and those who were normal or low on trait anxiety (LTA, $n = 7$). In patients and age-matched female controls ($n = 10$), heart rate (HR), blood pressure (BP; Finapres device) and respiration were recorded during a period of supine rest (10 min), orthostatic challenge (60° head-up tilting, 8 min), and post-orthostatic supine rest (8 min). Power spectra were calculated over the last 4 min of these three situations for HR, systolic BP, as well as for respiration. Spectral density was assessed for three frequency bands: low (0.02–0.06 Hz), mid (0.07–0.14 Hz) and high (0.15–0.50 Hz). Patients did not differ from controls during supine rest. During orthostatic challenge, HTA patients showed significantly more HR increase and suppression of high-frequency fluctuations of HR (suggesting stronger vagal inhibition) in comparison with the controls; this effect was accompanied by a significant increase in respiratory frequency. Both patients groups did not show the normal increase in mid-frequency band fluctuations of BP during orthostatic challenge, indicating reduced sympathetic activation. Low-frequency fluctuations of HR, as well as respiratory frequency during post-orthostatic supine rest of the HTA patients were significantly increased versus controls. This exploratory study indicates that trait anxiety may be a relevant factor when evaluating parasympathetic and sympathetic dysbalances in the state of a major depressive disorder.

Keywords: Major depressive disorder; Trait anxiety; Cardiovascular variability; Spectral analysis

1. Introduction

Spectral analysis of beat-to-beat variations in heart rate (HR) and blood pressure (BP) can be applied as a useful non-invasive tool to describe sympathetic

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and parasympathetic processes within short-term cardiovascular neural control mechanisms (Akselrod et al., 1985; Malliani et al., 1991; Tulen, 1993). Three relevant spectral peaks are usually identified within a time period of several minutes, which are in strength of appearance dependent upon the posture of the subject (supine, standing, sitting): *a low-frequency peak* around 0.04 Hz: for HR this peak is associated with both parasympathetic and sympathetic activity, while low-frequency BP fluctuations are linked with variations in peripheral vasomotor activity (Akselrod et al., 1985); *a mid-frequency peak* around 0.1 Hz which for BP may be the result of a resonance in the baroreflex control of peripheral resistance, while the HR fluctuations at these frequencies represent a reflection of the baroreflex response (Baselli et al., 1988; Madwed et al., 1989). These mid-frequency fluctuations are often associated with sympathetic activity (Malliani et al., 1991), although HR fluctuations in this frequency range may also reflect parasympathetic activity (Pomeranz et al., 1985). The *high-frequency peak* is usually centered between 0.20–0.35 Hz: for HR these fluctuations primarily reflect respiratory linked variations (respiratory sinus arrhythmia) as a result of centrally mediated vagal (parasympathetic, i.e., cholinergic) control (Angelone and Coulter, 1964; Davies and Nielson, 1967). For BP these fluctuations are proposed to be primarily the result from the mechanical effects of respiration (Saul et al., 1991). In addition to spectral analysis, transfer function analysis can be utilized in order to assess the dynamics of relationship between cardiovascular parameters in the frequency domain (Robbe et al., 1987).

The technique of spectral analysis can therefore be employed to analyze autonomic dysbalances in psychiatric disorders with a prevalence of abnormalities of the autonomic nervous system, such as occurs in anxiety or depressive disorders (e.g., Rudorfer et al., 1985; Stein et al., 1992). At this moment, research on the combined (spectral) analysis of HR and BP variability in psychiatric disorders is scarce: most studies on psychiatric disorders have focused on time domain measures of HR variability, respiratory sinus arrhythmia, or spectral analysis of HR variability. Decreased heart rate variability has been reported in depressive disorder (Dalack and Roose, 1990; Miyawake and Salzman, 1991; Rechlin et al., 1994), but conflicting findings do exist (Yeragani et al., 1991). Decreased HR variability as a result of diminished cardiac vagal activity has been shown to be a strong predictor of sudden death in patients with myocardial infarction (Bigger et al., 1993; Kleiger et al., 1987). Because an increased incidence of mortality by cardiovascular diseases has been observed in depressive disorders (e.g., Black et al., 1985; Malzberg, 1937), these findings suggest that decreased HR variability may predispose patients with depressive disorders to increased risk of cardiovascular mortality. However, other studies point to the specificity of diminished HR variability (especially high-frequency variability) for patients with panic disorder (Yeragani et al., 1990, 1993). Diminished HR variability has also been found in subjects with non-clinical panic attacks (Friedman et al., 1993); the reduced high-frequency variability may occur in combination with an increase in mid-frequency variability of HR (increased sympathetic tone) during specific situations (Friedman et al., 1993; Yeragani et al., 1993). However, for an accurate interpretation of spectral peaks in terms of sympathetic and parasympathetic cardiovascular control mechanisms a combined analysis of HR and BP fluctuations seems warranted (Tulen et al., 1994), while an additional control for respiratory frequency may be essential (Grossman and Kollai, 1993).

There exists a large body of research on the link between anxiety and heart rate reactivity and much less consistent cardiovascular studies of depressed subjects. It has been assumed that substantial subgroups of depressed patients concurrently suffer from prominent symptoms of anxiety, which may explain the occasional parallels between cardiovascular studies in depressed and anxious patients (Stein et al., 1994). Anxiety and depressive symptoms are known to frequently coexist to varying degrees within major depressive disorder, generalized anxiety disorder or panic disorder (Shores et al., 1992; Stavrakaki and Vargo, 1986). In addition, personality traits such as emotional strength or neuroticism have been found to be related to the occurrence of depressive episodes (Hirschfeld et al., 1989). In order to explore the anxiety-depression relationship in connection with anxiety-related personality traits and cardiovascular reactivity, we studied the relationship between trait anxiety and cardiovascular variability during the state

of a major depressive episode in hospitalized patients. The patients in this study had no concomitant anxiety disorders during their depressive episode. We divided our patient sample into two groups: those who were found to be high on trait anxiety and those who were normal or low on trait anxiety. With this approach we explored if anxiety, particularly trait anxiety, may explain some of the parallels in cardiovascular responses between anxiety and depressive disorders during a situation of supine rest and a situation of autonomic nervous system activation (orthostatic challenge). Because Yeragani et al. (1991) observed that panic disorder patients also showed abnormal orthostatic reflexes from standing to supine posture, we also included the post-orthostatic supine rest period in our analysis.

2. Methods

2.1. Patients and controls

The cardiovascular data were derived from a study to the effects of different antidepressants on hemodynamic parameters in depressed patients (Tulen et al., 1996). Because the majority of the depressed patients in this study consisted of women, we restricted our analysis to female patients and age-matched female controls only, in order to exclude sex-related cardiovascular effects. Sixteen female hospitalized unipolar depressed patients (mean age 51.2 years, SD 7.7, range 36–64 years) and 10 age-matched female controls (mean age 51.8 years, SD 9, range 38–64 years) were studied. The study was approved by the Medical Ethical Review Committee of the University Hospital Rotterdam Dijkzigt. Patients and controls gave written informed consent before the start of the protocol.

After an extensive psychiatric and medical screening, two senior psychiatrists diagnosed the patients according to the criteria of the DSM-III-R (American Psychiatric Association, 1987). The psychiatric interview included the Hamilton Rating Scale (HRS; Hamilton, 1967), the Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer et al., 1978) and the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979). Only patients with a diagnosis 'major depressive episode' and an initial score on the HRS of > 18 were included in the study. Specific exclusion criteria were: organic deficits, use of drugs such as antihypertensives, pregnancy and epilepsy. Based on psychiatric and medical history information, and an interview with first-degree relatives or partner, the patients for this exploratory cardiovascular study were diagnosed as either high on trait anxiety (HTA), or normal or low on trait anxiety (LTA). For this purpose, a 34 item questionnaire regarding trait anxiety was developed, which comprised the SADS items on anxiety disorders and items related to aspects of psychic anxiety (e.g., nervousness, anxious feelings, fear of dying, irritability, impatience, concentration disturbances, depersonalization, indecisiveness) and somatic anxiety (e.g., restlessness, trembling, muscle tension, insomnia, shortness of breath, chest pain, palpitations, abdominal distress, dizziness, sweating). Both presence and intensity of these aspects of anxiety were quantified. The two psychiatrists had to agree on the diagnosis of the patients: 7 patients were diagnosed as LTA patients, 9 patients were diagnosed as HTA. The patients had no concomitant anxiety disorders during their depressive episode. The patient groups did not differ regarding their score on the HRS (LTA: 25.6 ± 3.5; HTA: 27.8 ± 4.4) or the MADRS (LTA: 34.4 ± 4.4; HTA: 37.0 ± 5.0).

Based on medical history information and present state physical and mental condition (established by interview), the female controls appeared in good health and were normal to low on trait anxiety. Control subjects with a personal history of psychiatric illness and a positive psychiatric family history were excluded from the study.

2.2. Design and procedure

The patients were studied after a drug-free period of at least 7 days, before they started treatment with antidepressants. In the washout/observation period of 2 weeks preceding the baseline week, 8 of the 16 patients were free of psychoactive drugs, 6 patients received incidental treatment with an anxiolytic (lorazepam), 3 patients had received a single dose of neuroleptics (haloperidol, lithium), whereas on entering the washout period 5 patients were treated for several days (max 2) with antidepressants

(moclobemide, clomipramine, imipramine, amitryptiline, mianserine). The control subjects were drug-free during the study and had been for at least 3 weeks prior to the study.

The recording sessions were always performed between 9.30 and 12 a.m. To avoid hypoglycemic effects, the subjects were asked to take their normal breakfast on each study day, without coffee. Coffee and smoking were not allowed before or during the recordings. During the recording session, the subjects rested supine on a tilt-table in a quiet experimental room. After a stabilization period (of at least 15 min), recordings were obtained during: supine rest (10 min), orthostatic challenge (8 min), and post-orthostatic supine rest (8 min). During supine rest, spontaneous fluctuations in breathing, heart rate and blood pressure were recorded: the subjects were asked to relax, not to speak and move as little as possible, and to stay awake. The orthostatic challenge test was performed by 60° head-up tilting by means of the tilt-table. During the post-tilting period, spontaneous fluctuations in breathing, heart rate and blood pressure were again recorded.

2.3. Recordings

ECG, blood pressure and respiration were recorded continuously during the sessions on a multichannel FM-type analogue recorder (Racal Store 14 DS, Sarasota, FL, USA) for off-line analyses per computer. The ECG was derived using a precordial lead, amplified by means of a polygraph (Nihon Kohden, Tokyo, Japan). Blood pressure was recorded using a servo-plethysmo-manometer for continuous non-invasive measurement of finger arterial blood pressure, employing the volume clamp technique of Penaz (Penaz et al., 1976; Settels and Wesseling, 1985) (Finapres 2300 NIBP monitor, Ohmeda, Englewood, CO, USA). Thoracic and abdominal respiration were measured separately by means of impedance plethysmographs (Nihon Kohden, Tokyo, Japan).

2.4. Analysis

The ECG, blood pressure and respiration signals were digitized at a sample frequency of 1024 Hz on a Personal Computer (Dell optiplex 466/L) connected to an Analogue/Digital converter (Advantech PC-LabCard model PCL-718). R-R intervals in the ECG were detected with an accuracy of 1 ms and transposed to heart rate (HR) series. Systolic and diastolic blood pressure (SBP, DBP) were defined per R-R interval of the ECG.

2.4.1. Spectral analysis

Two consecutive periods of 4 min (240 s) during supine rest, two consecutive 4 min periods during orthostatic stress and two consecutive periods of 4 min during post-orthostatic supine rest of HR-, SBP- and DBP-time series were subjected to a discrete Fourier transform, based on non-equidistant sampling of the R-wave incidences (CARSPAN program, Mulder et al., 1988; Van Steenis et al., 1994). For each 4-min time-segment, the power was calculated for the total band (0.02–0.50 Hz), low-frequency band (0.02–0.06 Hz), mid-frequency band (0.07–0.14 Hz) and high-frequency band (0.15–0.50 Hz), in addition to mean HR, SBP and DBP, variation coefficient of HR, SBP and DBP. Spectral power for each selected frequency band was expressed in relative terms, i.e., as fraction of the mean value of the considered signal (squared modulation index, Van Dellen et al., 1985). The spectral power data were transformed to natural logarithmic values because of skewness of the distributions.

As an index of baroreflex sensitivity, we computed per time segment the gain (or modulus) in the mid-frequency band and the high-frequency band between the SBP values and the R-R interval times, based on those frequency points within the 0.07–0.14 Hz range and within the 0.15–0.50 Hz range with a coherence between the two signals of greater than or equal to 0.35 (Robbe et al., 1987).

2.4.2. Respiration

Per time-segment, samples of the respiratory signal were obtained at each incidence of the R-wave (Mulder, 1988). Subsequently, these respiratory time-series were subjected to spectral analysis, in a similar approach as described above (Mulder et al., 1988). Per time-segment, the dominant peak in the power spectrum was assessed.

2.5. Statistical analysis

Data will be presented as mean (±SD), for the patient groups (LTA, $n = 7$; HTA, $n = 9$) and for the controls ($n = 10$), separately. Cardiovascular variability during supine rest (4 min-period before tilting) was compared with cardiovascular variability during orthostatic challenge (stabilized part: last 4 min-period during tilting) and cardiovascular variability during post-orthostatic supine rest (stabilized part: last 4-min period). Because variability data of DBP were similar to that of SBP, only SBP variability data are presented. Within each group, effects of orthostatic challenge and post-orthostatic supine rest were evaluated by means of paired Student's *t*-tests. For the cardiovascular parameters, between group comparisons were made by means of one-factor (factor GROUP: LTA/HTA/controls) analysis of variance (ANOVA), for the three situations (supine rest, orthostatic challenge, post-orthostatic supine rest) separately. A multiple range test (Scheffe) was applied in order to describe significances between the three groups after a significant main effect was found with the ANOVA. A *P*-value of < 0.05 was used to indicate a significant effect.

3. Results

3.1. Cardiovascular variability

3.1.1. Supine rest (Tables 1–3)

Both patient groups did not differ significantly from each other or from the controls on any of the cardiovascular parameters during supine rest.

3.1.2. Orthostatic challenge (Tables 1 and 3; Fig. 1 and Fig. 2)

Within-group effects. Orthostatic challenge in the *normal controls* induced the following significant effects: HR and DBP increased (Table 1), as well as mid- and high-frequency band log power of SBP. Orthostatic challenge reduced the modulus in the controls; the effect was only significant for the high-frequency band ($P < 0.05$; Table 3). *The LTA patient group* showed a significant HR increase, accompanied by a significant decrease in mid- and high-frequency band log power of HR. In addition, high-frequency band log power of SBP increased, as well as DBP (Table 1). The modulus of the high-frequency band decreased significantly ($P < 0.01$) in the LTA depressed patients (Table 3). During ortho-

Table 1
Mean (SD) of the cardiovascular parameters during supine rest and orthostatic challenge for the patients who were high on trait anxiety (HTA), the patients who were normal or low on trait anxiety (LTA) and the control group

	Supine rest			Orthostatic challenge			Rest vs. Challenge (paired *t*-test; *P* values)		
	Controls	LTA	HTA	Controls	LTA	HTA	Controls	LTA	HTA
HR (bpm)	65 (5)	72 (14)	72 (14)	69 (7)	80 (13)	86 (15) *	0.025	0.007	0.001
CVHR (%)	5.2 (2)	4.1 (2)	4.6 (2)	4.5 (2)	3.3 (1)	3.0 (2)	NS	NS	0.014
LFB HR	6.4 (1)	6.0 (1)	6.4 (1)	6.5 (1)	5.8 (1)	5.6 (1)	NS	NS	NS
MFB HR	6.0 (1)	5.8 (1)	5.9 (1)	5.9 (1)	5.2 (1)	4.9 (1)	NS	0.020	0.019
HFB HR	6.0 (1)	5.8 (1)	5.9 (1)	5.6 (1)	4.9 (1)	4.1 (1) **	NS	0.001	0.001
SBP (mmHg)	118 (19)	134 (31)	122 (21)	119 (22)	134 (26)	124 (22)	NS	NS	NS
CVSBP (%)	5.2 (3)	5.3 (2)	4.4 (1)	5.3 (1)	4.7 (2)	4.2 (1)	NS	NS	NS
LFB SBP	6.5 (1)	6.4 (1)	6.3 (0)	6.6 (1)	6.3 (1)	6.2 (1)	NS	NS	NS
MFB SBP	5.3 (1)	5.5 (1)	5.1 (1)	5.9 (1)	5.6 (1)	5.6 (1)	0.050	NS	NS
HFB SBP	4.7 (1)	4.7 (1)	4.7 (1)	5.1 (1)	5.5 (0)	5.0 (1)	0.028	0.050	NS
DBP (mmHg)	65 (13)	70 (17)	68 (11)	70 (13)	78 (18)	77 (12)	0.006	0.004	0.007

* ANOVA *F* value: 5.2, $P < 0.01$; Scheffe test: HTA ≫ controls).
** ANOVA *F* value: 4.0, $P < 0.03$; Scheffe test: HTA ≪ controls).
CV, variation coefficient; LFB, low frequency band (log power); MFB, mid-frequency band (log power); HFB, high-frequency band (log power).

Table 2
Mean (SD) of the cardiovascular parameters during post-orthostatic (post-tilt) supine rest, of the patients who were high on trait anxiety (HTA), the patients who were premorbidly normal or low on trait anxiety (LTA) and the controls

	Post-tilt supine rest			Tilt vs. Post-tilt supine rest (paired t-test; P values)		
	Controls	LTA	HTA	Controls)	LTA	HTA
HR (bpm)	60 (5)	69 (14)	69 (14)	0.001	0.005	0.001
CVHR (%)	4.7 (2)	6.6 (2)	5.7 (1)	NS	0.013	0.002
LFB HR	6.1 (1)	6.5 (1)	7.1 (1) *	NS	0.042	0.019
MFB HR	5.8 (1)	6.4 (1)	6.6 (1)	NS	0.021	0.012
HFB HR	6.4 (1)	6.7 (2)	6.2 (1)	0.012	0.005	0.001
SBP (mmHg)	126 (16)	141 (25)	131 (22)	NS	0.024	NS
CVSBP (%)	4.9 (1)	5.3 (4)	5.0 (2)	NS	NS	NS
LFB SBP	6.6 (1)	6.6 (2)	6.7 (1)	NS	NS	0.040
MFB SBP	5.4 (1)	5.5 (1)	5.6 (1)	0.009	NS	NS
HFB SBP	4.7 (1)	4.9 (1)	4.9 (1)	NS	0.017	NS
DBP (mmHg)	67 (11)	72 (19)	72 (10)	0.038	0.022	0.026

* ANOVA F value: 3.6, $P < 0.04$; Scheffe test: HTA ≫ controls).

static challenge in *the HTA patient group*, HR increased significantly, while the variation coefficient of HR, and mid- and high-frequency band log power of HR decreased (Table 1). In the HTA patient group, BP was not influenced by orthostatic challenge, with the exception of the increase in DBP.

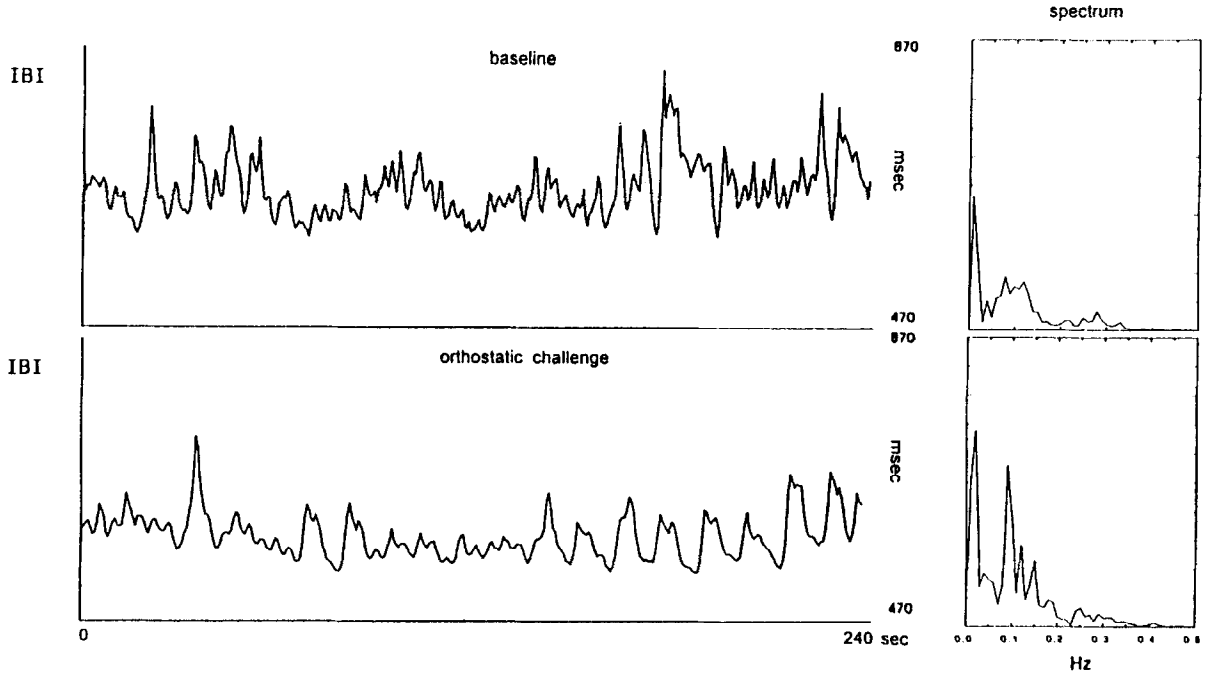

Fig. 1. Example of spontaneous fluctuations in interbeat intervals (IBI) of a female subject (38 years) during a 4-min period of supine rest (upper figure) and orthostatic challenge (lower figure), as well as the reflection of these variations in the power spectra. y-axis spectra: spectral power ranged from 0.0 to 1.0×10^5 (squared modulation index: Mulder, 1988).

Table 3
Mean (SD) modulus (ms/mmHg) of the mid (MFB) and high (HFB) frequency bands, during supine rest, orthostatic challenge and post-orthostatic supine rest

	Modulus (ms/mmHg)	
	MFB(0.07–0.14 Hz)	HFB(0.15–0.50 Hz)
Supine rest		
Controls	9.5 (4)	14.0 (7)
LTA	8.6 (7)	10.2 (6)
HTA	11.6 (10)	11.0 (6)
Orthostatic challenge		
Controls	6.9 (4)	7.8 (3)
LTA	4.1 (3)	3.5 (1) *
HTA	4.4 (3)	3.7 (3) *
Post-orthostatic rest		
Controls	9.5 (4)	15.3 (7)
LTA	9.9 (6)	11.2 (6)
HTA	11.0 (5)	11.1 (5)

* ANOVA F value: 6.5, $P < 0.006$; Scheffe test: patients, LTA and HTA ≪ controls).

Both the modulus of the mid- and the high-frequency band decreased significantly (both $P < 0.01$; Table 3).

Between-group effects. HR and high-frequency band log power of HR of the HTA patients differed significantly from the controls (Table 1): HTA patients showed more HR increase and a more suppression of high-frequency band variability. Both patient groups showed a significantly lower modulus of the high-frequency band (Table 3), when compared with the controls.

Table 4
Mean (SD) respiratory frequency (Hz), during supine rest, orthostatic challenge and post-orthostatic supine rest

	Resp. freq. (Hz)
Supine rest	
Controls	0.23 (0.05)
LTA	0.26 (0.04)
HTA	0.28 (0.05)
Orthostatic challenge	
Controls	0.24 (0.03)
LTA	0.28 (0.06)
HTA	0.31 (0.04) *
Post-orthostatic rest	
Controls	0.22 (0.03)
LTA	0.25 (0.05)
HTA	0.29 (0.04) * *

* ANOVA F value: 5.2, $P < 0.021$; Scheffe test: HTA ≫ controls).
* * ANOVA F value: 5.6, $P < 0.014$; Scheffe test: HTA ≫ controls).

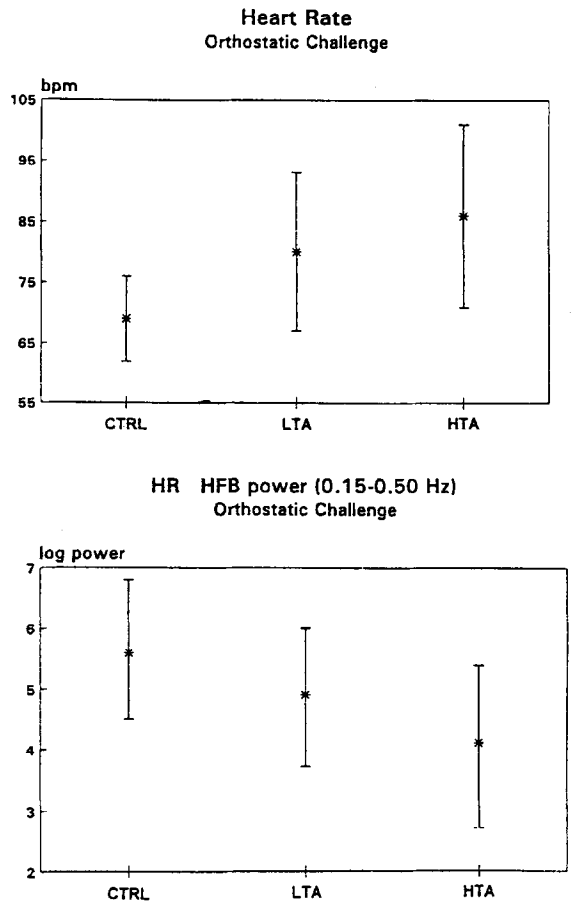

Fig. 2. Mean (±SD) heart rate (upper figure) and high-frequency band log power of HR (lower figure) during orthostatic challenge for the control group (ctrl) and the patients high on trait anxiety (HTA) and normal or low on trait anxiety (LTA).

3.1.3. Post-orthostatic supine rest (Tables 2 and 3)

Within-group effects. Supine rest after orthostatic challenge in the controls significantly lowered HR and DBP, increased high-frequency band fluctuations of HR and the modulus of the high-frequency band ($P < 0.01$; Table 3), and reduced mid-frequency fluctuations of SBP (Table 2). In both patient groups, all HR parameters, as well as DBP, changed significantly: HR and DBP decreased, whereas all frequency fluctuations of HR increased (Table 2), in

addition to the modulus of the mid- and high-frequency bands (both $P < 0.01$; Table 3). In the LTA patient group, these effects were accompanied by a significant increase in SBP and a significant decrease in high-frequency fluctuations of SBP. In the HTA patient group, low-frequency fluctuations increased significantly.

Between-group effects. ANOVA-analyses revealed only one significant effect: low-frequency band fluctuations were significant increased in the HTA patients as compared with controls (Table 2).

3.2. Respiration (Table 4)

Although respiratory frequency during supine rest tended to be higher for both patient groups, these findings were not significant versus the controls. During orthostatic challenge, respiratory frequency was significantly higher in the HTA patients, as compared with the controls. Also during post-orthostatic supine rest, the HTA patients showed a significantly higher respiratory frequency than the controls.

4. Discussion

In this study, female patients with a major depressive episode differed from controls only in their response to orthostatic challenge and post-orthostatic supine rest: the differences were strongest for the patients who were high on trait anxiety.

4.1. Orthostatic challenge

The patient groups differed from the controls in their response to orthostatic challenge in two ways: (1) In both groups, mid- and high-frequency variations of HR decreased upon standing, whereas this effect was not observed for the control subjects. Young healthy subjects usually show an increase in mid-frequency HR variations and a decrease in high-frequency HR variations after orthostatic challenge (Weise et al., 1987). However, these effects are diminished in older subjects (Lipsitz et al., 1990), as we observed in this study. The reduction in HR variations points to a strong vagal inhibition during orthostatic challenge in both patient groups. (2) The patients did not show the normal increase in mid-frequency band fluctuations of BP during orthostatic challenge (Pagani et al., 1986). This points to a reduced sympathetic activation during orthostatic stress in the patients. Due to baroflex regulatory mechanisms, this diminished increase in mid-frequency BP variations may also be responsible for the reduction of mid-frequency HR variations in both patient groups (Baselli et al., 1988; Madwed et al., 1989).

Between-group comparisons revealed that the HTA patients showed significantly more HR increase and decrease in high-frequency fluctuations of HR (suggesting stronger vagal inhibition) in comparison with the controls; the decrease in high-frequency band power of HR in the HTA patients during orthostatic challenge was partly explained by an increase in respiratory frequency; an effect caused by the rhythmic respiratory synchronous modulation of cardiac vagal nerve activity (Spyer, 1982). Both patient groups showed a significantly reduced modulus of the high-frequency band (index of baroreflex sensitivity), in comparison with the controls. This effect underlines the strong vagal inhibition in the patient groups upon standing: a decrease in baroreflex sensitivity may be the result of parasympathetic inhibition (Eckberg et al., 1971).

Between-group comparison revealed no differences regarding overall BP levels or BP variability between the three groups, suggesting that BP parameters are less relevant for discrimination among groups on basis of trait anxiety. In general, clear differences regarding overall BP levels during supine rest and orthostatic challenge between depressed patients and controls are not reported in the literature (i.e., Roy et al., 1985; Rudorfer et al., 1985). However, the lack of a significant increase in mid-frequency BP fluctuations upon passive standing in both patient groups does suggest the presence of impaired sympathetic regulatory processes. It is not clear how this finding relates to the exaggerated orthostatic responsivity of plasma noradrenaline as observed in depressed patients (Rudorfer et al., 1985), although increased peripheral noradrenaline concentrations can induce a reflex mediated suppression of mid-frequency BP fluctuations (Tulen et al., 1994).

4.2. Post-orthostatic supine rest

HTA and LTA patients differed from the controls in the sense that both groups showed a significant

increase of HR variability upon changing from standing to supine posture without clear changes in BP variability, suggesting a predominant cardiac vagal increase. Between group comparisons revealed that low-frequency fluctuations of HR as well as respiratory frequency during post-orthostatic supine rest of the HTA patients were significantly increased versus the controls, thereby underlining a more extreme response for the HTA patients.

In general, our data indicate an impairment of the orthostatic reflex in depressed patients with a prevalence of parasympathetic dysfunctions over sympathetic dysfunctions, although at present it is not clear whether this finding is restricted to the depressed state or whether it persists when the patients are no longer depressed. Furthermore, it can not be excluded that possible differences between patients and controls regarding effects of nicotine and caffeine dependency have contributed to the results. Our HR findings are in line with previous reports of reduced HR variability in depressive disorder (Dalack and Roose, 1990; Miyawake and Salzman, 1991, Rechlin et al., 1994), but contradictory to the findings of Yeragani et al. (1991). Age-related cardiovascular effects may possibly explain some of the differences between our study and Yeragani's: our depressed patients were on average 20 years older than their patient sample.

Vagal inhibition upon passive standing and vagal stimulation during post-orthostatic supine rest, as presented by changes in HR variations, were strongest in the patients who were high on trait anxiety. We found that at least part of these effects could be explained by changes in respiratory frequency, possibly related to a hyperventilation-like response of these patients to orthostatic stress. Our respiratory analysis technique did not allow a detailed evaluation of respiratory dynamics in order to verify this reliably. It is, however, not unlikely that the orthostatic reflexes themselves have been influenced by these anxiety-related respiratory phenomena.

Our data of the HTA depressed patients match some of the data of patients with panic disorder (Yeragani et al., 1990, 1991; Stein et al., 1992). In fact, although there are some differences in design and mean age of the patient groups, regarding overall HR variability and high frequency band HR fluctuations we observed a rather close match with the panic disorder data of Yeragani et al. (1990, 1991, 1993), both during and after orthostatic challenge. We evaluated our patients, all with a major depressive episode but without concomitant anxiety disorders, into two groups: those who were clearly high on trait anxiety and those who were not. In this 'forced-choice' method we did not allow an intermediate group with dubious cases. The LTA patients showed, regarding HR variability, an intermediate pattern between controls and HTA patients. Further studies with more patients are required to determine whether this intermediate pattern reflects anxiety-related aspects which we ignored in some patients, or whether these patterns occur in the state of a depressive episode, unrelated to anxiety. Also, we did not focus on state-anxiety aspects, although this may have been relevant for the cardiovascular responses we observed. Nevertheless, our cardiovascular findings suggest that in the exaggerated heart rate responses to orthostatic challenge as observed in both anxiety and depressive disorders, personality factors such as trait anxiety may play an important role.

4.3. In conclusion

Although only a limited number of patients were involved in this exploratory study and our analysis were restricted to females only, our data confirm and extend previous observations regarding the presence of autonomic dysfunctions in unmedicated depressed patients: spectral analysis of HR and BP fluctuations revealed that both parasympathetic and sympathetic mechanisms are involved, specifically during orthostatic challenge and post-orthostatic supine rest. Differences with the controls were significant only for the patients who were high on trait anxiety, suggesting that trait anxiety is a relevant factor to consider when explaining autonomic dysbalances in major depressive disorder.

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