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Effects of lorazepam on cardiac vagal tone during rest and mental stress: assessment by means of spectral analysis

J.H.M. Tulen[1,2], G. Mulder[3], L. Pepplinkhuizen[1,2], A.J. Man in 't Veld[4], H.G. van Steenis[2,5], P. Moleman[1]

[1] Department of Psychiatry, University Hospital Rotterdam Dijkzigt and Erasmus University Rotterdam, Dr. Molewaterplein 40, NL-3015 Rotterdam, The Netherlands
[2] Section Pathophysiology of Behavior, Erasmus University Rotterdam, The Netherlands
[3] Department of Experimental Psychology, University of Groningen, The Netherlands
[4] Department of Internal Medicine, University Hospital Rotterdam Dijkzigt, The Netherlands
[5] Department of Clinical Neurophysiology, University Hospital Rotterdam Dijkzigt, The Netherlands

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Abstract. Dose-dependent effects of intravenously administered lorazepam on haemodynamic fluctuations were studied by means of spectral analysis, in order to elucidate sympathetic and parasympathetic components in cardiovascular control during situations of rest and mental stress after benzodiazepine administration. In a double-blind randomized cross-over study, nine male volunteers participated in two sessions: a placebo and lorazepam session. During these sessions, the subjects repeatedly performed a 10-min version of the Stroop Color Word Test (CWT), with 10 min of rest between the CWTs. Lorazepam was administered before each rest period in increasing doses of 0.0, 0.06, 0.13, 0.25 and 0.5 mg (total cumulative dose: 0.94 mg). During the placebo session the subjects received five placebo injections. For five of the nine subjects the lorazepam session was their first session. Heat rate (HR), blood pressure (BP) and respiration were recorded continuously. Power spectra were calculated per 2.5-min periods for HR, systolic (SBP) and diastolic BP (DBP). Spectral density was assessed for three frequency bands: low (LFB: 0.02–0.06 Hz), mid (MFB: 0.07–0.14 Hz) and high (HFB: 0.15–0.40 Hz). During the consecutive periods of rest, lorazepam induced a dose-dependent decrease in HR, and a dose-dependent increase in LFB, MFB and HFB power of HR, but lorazepam had no effect on BP. The effects were significant after 0.44 mg lorazepam for HR and HFB power, and after 0.94 mg lorazepam for the HR fluctuations in the LFB and MFB. Lorazepam did not influence the cardiovascular responses to the CWT. Our data underline that benzodiazepines can exert a specific influence on parasympathetic activity: lorazepam induced dose-dependent increases in cardiac vagal tone, resulting in decreased HR and increased HR variability, but only during periods of rest. The increase in vagal tone observed after low doses of lorazepam was not related to diminished sympathetic activity, altered respiration, or increased sedation.

Correspondence to: J.H..M. Tulen

Key words: Intravenous lorazepam – Spectral analysis – Cardiac vagal tone – Cardiovascular variability

Benzodiazepines are the preferred drugs in the treatment of anxiety symptoms in patients with cardiovascular dysfunction. The effects of benzodiazepines on autonomic cardiovascular control mechanisms in man have been studied and interpreted primarily in relation to sympathetic nervous system activity (Duka et al. 1986; Marty et al. 1986; Roy-Byrne et al. 1988; Tulen et al. 1991) and not to parasympathetic mechanisms.

Normal vagal (parasympathetic) cardiac control has been associated with good health (Eckberg 1980). Since Epstein et al. (1973) observed that in patients with an acute myocardial infarction the vagal tone to the heart exerts a significant protective effect against lethal ventricular arrhythmias, a careful evaluation of the vagolytic or vagomimetic properties of anxiolytic drugs seems warranted. Animal research has suggested that benzodiazepines can affect cardiac vagal tone by means of GABA-ergic inhibitory mechanisms (DiMicco 1987).

Analysis of variation patterns in cardiovascular parameters such as heart rate (HR) or blood pressure (BP) offers one approach to obtaining non-invasive indices of cardiac parasympathetic activity. Previous research has shown that breathing linked variations in HR reflect a parasympathetic influence on the heart by means of alterations in cardiac vagal inhibition (Higgins et al. 1973; Katona and Jih 1975; Eckberg 1985). In a recent study by Adinoff et al. (1992) cardiac vagal tone, as determined by quantifying the amplitude of the respiratory sinus arrhythmia, was found to decrease after intravenous administration of diazepam. This finding in human subjects therefore indicates a specific parasympathetic effect of benzodiazepines, but further studies in human subjects are needed to substantiate this.

Previously, we have reported the dose-response effects (dose range: 0.0–0.94 mg) of cumulative intravenous doses of lorazepam on sympathetic nervous system activity and psychological parameters (Tulen et al. 1991). We observed a significant decrease in heart rate at low doses of lorazepam (ED_{50}: 0.13 mg) during periods of rest, whereas sedation and suppression of sympathetic parameters occurred at a significantly higher cumulative dose of 0.94 mg. We suggested that this may reflect an increase in vagal stimulation of the heart, but were unable to substantiate this. We have now analyzed the data of the above mentioned experiment by means of spectral analysis of beat to beat fluctuations in HR and BP. With this method three spectral peaks are usually defined within a time segment of several minutes (Sayers 1973; Akselrod et al. 1981, 1985):

1. A low frequency peak with variations around 0.04 Hz; for HR this peak is associated with both parasympathetic and sympathetic activity (Akselrod et al. 1985), while these low-frequency BP fluctuations are linked to variations in peripheral vasomotor activity due to thermoregulatory influences (Kitney 1975) or renin-angiotensin system activity (Akselrod et al. 1985).
2. A mid frequency peak with variations around 0.1 Hz (Mayer waves) which has been associated with changes in sympathetic tone (Pagani et al. 1986), or with a resonance in the baroreflex control of peripheral resistance (Wesseling and Settels 1985; Madwed et al. 1989).
3. A high frequency peak around the respiratory frequency, usually between 0.20 and 0.35 Hz, which for HR represents centrally mediated vagal (parasympathetic) activity (Angelone and Coulter 1964; Davies and Nielson 1967). For BP these fluctuations may result from centrally mediated HR fluctuations (Akselrod et al. 1985), although the mechanical effects of respiration may also contribute substantially to these fluctuations (Saul et al. 1991).

This means that spectral analysis can be employed to obtain non-invasive estimates of both sympathetic and parasympathetic activity within short-term cardiovascular control, and as such it may extend our insight into the effects of benzodiazepines on autonomic nervous system activity during various situations of rest or stress and anxiety. Beat to beat fluctuations in HR and BP are now widely studied to quantify parasympathetic and sympathetic influences within the complex neural control of short-term homeostatic cardiovascular processes (i.e. Akselrod et al. 1981, 1985; Yongue et al. 1982; Pomeranz et al. 1985; Malliani et al. 1991). In addition to these analyses of cardiovascular variability, we also analyzed baroreflex sensitivity according to the method described by Robbe et al. (1987).

The Stroop Color Word Test (CWT) was used in order to compare the effects of lorazepam during periods of rest and during periods of increased HR and BP due to mental stress as induced by the CWT (Frankenhaeuser and Johansson 1976; Hjemdahl et al. 1984; Tulen et al. 1989, 1991).

Materials and methods

Subjects. Nine male volunteers (mean age: 23.9 years; range: 21–29) each participated in two sessions in a randomized double-blind cross-over study, after they had given written informed consent. The study procedures and protocol were approved by the Medical Ethical Committee of the University Hospital Rotterdam Dijkzigt. The screening procedure included a medical examination to exclude subjects with cardiorespiratory abnormalities. All subjects were in good physical condition. Subjects with a history of alcohol or drug abuse were excluded from the study.

Design, procedure and measurements. Details of the procedures have been presented before (Tuien et al. 1991). During both sessions, the subjects performed on five consecutive occasions a 10-min version of the Stroop Color Word Test (CWT), with 10 min of rest between the CWTs. The CWT consists of four words (red, green, blue, yellow) which are presented on videotape, one word at a time, in four different colors (red, green, blue, yellow). The subject has to indicate the color of the word on an answer sheet, with the specific request to do his best and make as few errors as possible. The test induces cognitive conflict (Stroop 1935), while time-pressure effects are added due to the rapid presentation of the stimuli (on average one word per 1.5–2 s). In order to become familiar with the requirements of the task, a 2-min practice tape was presented at the beginning of the first session for instruction purposes.

During one session (the placebo or PLA session), an intravenous PLA injection (2.5 ml saline, slowly injected over 1 min) was administered five times, each time before the rest periods. During the other session (the lorazepam or LOR session), LOR was administered intravenously (in 2.5 ml saline, slowly injected over 1 min) before each rest period in increasing doses of 0.0, 0.0625, 0.125, 0.25 and 0.5 mg (total cumulative dose: 0.9375 mg). The two sessions per subject were recorded on separate days, 1 week apart. Five of the nine subjects received lorazepam during their first session. Each session lasted from 09:00 to 12:30 hours. Physiological, biochemical and psychological measurements were obtained while the subjects were seated in a comfortable armchair during the entire recording.

Forty-five minutes before the start of the recordings, a catheter Venflon, 18G, Viggo AB, Helsingborg, Sweden) was inserted into an antecubital vein of the non-dominant forearm, through which blood samples were drawn and infusions of LOR/PLA were given. Blood samples for assay of lorazepam concentrations were obtained 15 min after the injections (i.e. during the second half of each CWT: the last 5 min). Blood was collected in heparinized tubes; the tubes were immediately placed on ice and centrifuged within 15 min after collection. Plasma was subsequently frozen at $-70°$ C. Lorazepam was assayed with a high-performance liquid chromatographic method according to Brodie et al. (1978), with the following modifications: extraction with dichloromethane and a methanol/ammonium phosphate buffer (50/50) was used for elution of the column.

ECG, blood pressure and respiration were recorded continuously during the sessions on an FM-type analogue recorder (Racal Store 14 DS, Sarasota, Fla., USA) for off-line analyses by 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-plethysmomanometer for continuous non-invasive measurement of finger arterial blood pressure, employing the volume clamp technique of Peñáz (Peñáz et al. 1976; Settels and Wesseling 1985) (Finapres 2300 NIBP monitor, Ohmeda, Englewood, Col., USA). The cuffed middle finger of the non-dominant hand was kept at the level of the heart by means of a supportive arm-rest, in order to optimize the correspondence with intrabrachial pressure changes (Parati et al. 1989). Thoracic and abdominal respiration were measured separately by means of impedance plethysmographs (Nihon Kohden, Tokyo, Japan). Adhesive disposable Ag/AgCl electrodes (Red Dot, Medical Products Devision, 3M, St Paul, USA) were used for the thoracic and abdominal respiration recordings, placed at the level of the nipples and the abdomen, respectively.

Analyses. The ECG and blood pressure signals were digitized at a sample frequency of 1024 Hz on a Personal Computer (Commodore PC 60–III) 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, with an accuracy of 0.1 mmHg. For prolonged blood pressure recordings, the Finapres device has the facility of a built-in "lock-adjust" procedure for automatic adjustment of the finger cuff pressure by means of a servo system, which is activated in parallel with blood flow changes. This procedure takes place every 40–70 beats under stationary conditions. Since a total session in this study could last up to 3 h, we employed this procedure to prevent slow drifts and unreliable recordings. As a result, every 40–70 beats, 2–4 pulses were missing from the blood pressure recording. By means of a linear interpolation between two preceding and two succeeding pulses the missing values were estimated, while a small amount of additional noise (0.25 SD) was added in order to prevent a temporary excessive reduction in variability due to the correction procedure itself (Mulder 1988). In addition, time-series of HR, SBP and DBP were scrutinized for stationarity and artifacts by means of visual inspection. One blood pressure recording showed technical shortcomings and was not analyzed. The thoracic respiratory signal was sampled with a frequency of 102.4 Hz.

For each recording, the consecutive 10-min periods of rest were analyzed, in addition to the first 5 min of each CWT.

Spectral analysis of heart rate and blood pressure. Within each period of rest or CWT, consecutive time segments of 2.5 min 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). With this method power spectral densities of rhythmic oscillations over a frequency range of 0.02–0.50 Hz were obtained, with a frequency resolution of 0.01 Hz. For each time segment, power density was calculated for the total band (0.02–0.50 Hz), low frequency band (LFB: 0.02–0.06 Hz), mid frequency band (MFB: 0.07–0.14 Hz) and high frequency band (HFB: 0.15-0.40 Hz), in addition to mean HR, SBP and DBP, and variation coefficients (VC) of HR, SBP and DBP. Spectral energy was expressed in relative terms, i.e. in normalized values relative to the mean value of the considered signal (squared modulation index, to be compared with squared variation coefficient; Van Dellen et al. 1985). Because the total power equals the squared variation coefficient minus the low frequency DC component, total power data are not presented, but variation coefficients are. For the spectral data a logarithmic transformation was performed because of skewness of the distributions. As an index of baroreflex sensitivity (BRS), we computed per time segment the gain (or modulus) in the MFB between the systolic pressure values and the R–R interval times, based on those frequency points within the 0.07–0.14 Hz range with a coherence between the two signals of greater than or equal to 0.5 (Robbe et al. 1987).

The results of the analysis of the consecutive time segments (2.5-min periods) were averaged per rest or CWT period, because we observed no systematic trends within the concecutive time segments. This procedure reduced a noise factor due to spontaneous segment to segment fluctuations and allowed a statistical analysis of the dose- or time-dependent changes within the sessions.

Respiration. Mean (SEM) respiratory cycle duration (in seconds) and inspiratory depth (in percentage of change versus baseline times 100) were calculated per period of rest or CWT, on the basis of analysis of the thoracic respiratory signal. In addition, respiratory irregularities were quantified by computing the number of sighs (amplitude increase by a factor of 2, versus the mean amplitude of the previous 30 respiratory cycles) or hypopnoeas (amplitude decrease by a factor of 0.5) per period of rest or CWT.

Statistical analyses. Data will be presented as mean (SEM) for $n=9$ with the exception of the blood pressure analyses ($n=8$). Similarity of the baseline values of the two sessions was evaluated, per parameter, by means of t-tests for pairwise comparisons. Our analyses were focused at describing the dose-dependent effects during the LOR session, with the PLA session as a mere control. Therefore, MANOVAs for repeated measurements were performed for each condition separately. For the LOR condition, MANOVAs were used to establish the effect of the CWT versus the rest periods (within-subject Factor Stress: rest/CWT), the five doses of LOR (within-subject Factor Dose: five consecutive rest and CWT periods) and the interaction between factors Stress and Dose (reflecting the effect of increasing doses of lorazepam on the consecutive CWT responses, i.e. the CWT response magnitudes versus the preceding rest periods). For the PLA condition, the MANOVAs were employed to establish the effect of the CWT versus the rest periods (within-subject Factor Stress: rest/CWT), the time-dependency or habituation effects (within-subject Factor Time: five consecutive rest and CWT periods) and the interaction effect between factors Stress and Time (reflecting habituation effects in the consecutive CWT response magnitudes). If a significant main effect or interaction effect was observed, Duncan's multiple range tests were used in order to search for specific dose- or time-related effects. A P-value of <0.05 was used to indicate a significant effect.

Results

Plasma concentrations of lorazepam

The plasma LOR concentrations were proportional to the cumulative dose administered (Table 1).

Cardiovascular variability

For each cardiovascular parameter, baseline values of the PLA and LOR session were similar ($P>0.05$; NS).

Heart rate (HR). The CWT significantly increased HR and significantly decreased HR VC and fluctuations in the LFB, MFB and HFB during both the PLA and the LOR session (Tables 2, 3, Fig. 1). During the PLA session, the CWT response magnitudes showed no habituation during the five consecutive CWT presentations (no significant interaction effects, Table 2); significant time-dependent trends were only observed for the LFB fluctuations, showing a small gradual increase in power during the entire session (Table 2, Fig. 1). LOR induced a significant dose-dependent decrease in HR, while HR VC and LFB, MFB and HFB fluctuations increased dose-dependently (Table 2, Fig. 1, 3). Since no significant interaction effects between factors Stress and Dose for HR and LFB, MFB and HFB fluctuations were observed, it can be concluded that the resting values were affected by the increasing doses of LOR, while the response magnitudes to the consecutive CWTs remained the same. After a cumulative dose of 0.44 mg LOR, HR decreased and HFB fluctuations increased significantly compared with the first rest period. After a cumulative dose of 0.94 mg LOR, HR VC and fluctuations in LFB and MFB were significantly increased compared with the first rest period.

Systolic blood pressure (SBP). The CWT significantly increased SBP, and significantly decreased SBP VC and

Table 1. Mean (SEM) plasma concentrations of lorazepam after cumulative doses of LOR

Dose (mg)	Cumulative dose (mg)	Plasma LOR (ng/ml)
0	0	0
0.0625	0.0625	3.56 (0.44)
0.125	0.1875	6.22 (0.52)
0.25	0.4375	14.56 (3.54)
0.5	0.9375	20.00 (0.91)

LFB and MFB power during both the PLA and the LOR sessions (Table 2, 3, Fig. 2). During the PLA session, the fluctuations in the HFB were not significantly affected by the CWT ($P=0.09$, NS), but LOR significantly decreased HFB fluctuations during the CWT. During both sessions a significant decrease in the consecutive SBP CWT response magnitudes was observed (interaction effects significant), indicating learning or habituation effects to the CWT, but no drug-specific effects. During the PLA session we observed a time-dependent increase in SBP, which was not present during the LOR session (Table 2, Fig. 2). This increase in SBP during the PLA session was accompanied by a significant time-dependent decrease in VC and LFB fluctuations. LOR did not influence the CWT response magnitudes of SBP VC, and LFB, MFB and HFB fluctuations; these CWT responses also showed no habituation effects during the consecutive presentations (Table 2).

Diastolic blood pressure (DBP). The CWT significantly increased DBP and significantly decreased DBP VC and LFB, MFB and HFB fluctuations during both the PLA and the LOR session (Tables 2, 3). As with SBP, DBP increased time-dependently during the PLA session, while the consecutive CWT response magnitudes showed a habituation effect during both the PLA and the LOR session. The LFB fluctuations increased dose-dependently during the LOR-session (Tables 2, 3) due to a gradual increase in LFB power during the rest periods.

Baroreflex sensitivity. BRS decreased significantly during the CWTs of both the PLA and the LOR session (Tables 2, 4). The response magnitudes to the consecutive CWTs showed no time- or dose-dependent effects. However, during the LOR session the BRS levels during the rest periods increased dose-dependently; after a cumulative dose of 0.44 mg LOR, BRS was significantly increased compared with the first rest period.

Respiration

Respiratory cycle duration decreased significantly during the CWTs of the PLA and the LOR session (Tables 2, 4). During the PLA session this was accompanied by a significant reduction in respiratory depth; for the LOR session there was a trend towards significance (Table 2, $P=0.07$, NS). The number of sighs or hypopnoeas showed no systematic changes during the PLA or the LOR session because of highly variable data. Response magnitudes of the consecutive CWTs were not affected by LOR or PLA, for all the respiratory parameters measured.

Table 2. *F*-values and level of significancies of the MANOVAs for repeated measurements, for the placebo (*PLA*) and lorazepam (*LOR*) sessions separately. * $P<0.05$, ** $P<0.01$, *** $P<0.001$

	Placebo			Lorazepam		
	Stress (rest/CWT)	Time	Stress × Time (CWTresponse)	Stress (rest/CWT)	Dose	Stress × Dose (CWTresponse)
HR	12.82**	1.40	0.37	16.67**	12.04***	0.96
VC HR	29.54***	1.69	1.72	59.57***	15.23***	3.82**
LFB HR	25.87***	2.90*	0.45	37.83***	13.45***	0.58
MFB HR	42.52***	1.61	2.43	24.83***	8.68***	1.36
HFB HR	11.81**	0.74	1.10	34.04***	10.85***	0.67
SBP	12.39**	4.60**	3.15*	11.95**	0.53	7.13***
VC SBP	7.77*	5.12**	0.11	22.86**	1.70	0.44
LFB SBP	21.35**	4.98**	1.05	98.70***	0.38	0.04
MFB SBP	15.53**	0.96	0.50	17.48**	0.34	0.40
HFB SBP	3.78	1.89	1.24	39.26***	0.99	1.32
DBP	16.92**	5.68**	5.04**	32.06***	0.94	4.34**
VC DBP	13.42**	1.08	0.13	18.00**	2.03	0.27
LFB DBP	17.03**	0.62	0.60	54.66***	3.35*	0.18
MFB DBP	58.54***	2.36	0.15	27.53***	0.15	0.36
HFB DBP	05.87*	0.33	2.50	15.30**	0.88	0.48
BRS	10.89**	0.57	1.05	12.88**	7.14**	0.78
Resp. cycle	15.75**	0.68	0.95	28.38***	1.49	0.93
Resp. depth	6.60*	1.48	1.08	4.39	0.21	0.35
Sighs	2.97	2.60*	1.09	0.75	2.00	1.01
Hypopnoeas	0.04	2.00	0.99	0.45	0.83	0.55

Table 3. Mean (SEM) values of variation coefficients (*VC*) of HR, SBP and DBP and mean (SEM) values of DBP, and LFB, MFB and HFB log power of DBP during the consecutive rest and CWT periods, for the placebo (*PLA*) and lorazepam (*LOR*) sessions separately

		Rest1	CWT1	Rest2	CWT2	Rest3	CWT3	Rest4	CWT4	Rest5	CWT5	Rest6
VC HR (%)	PLA	8.3 (0.6)	6.3 (1.0)	9.8 (0.7)	5.9 (0.6)	9.6 (0.7)	6.6 (0.7)	10.7 (1.3)	7.2 (0.9)	10.8 (1.1)	7.0 (0.8)	10.2 (0.9)
	LOR	7.7 (0.9)	5.3 (0.4)	8.7 (0.9)	5.5 (0.6)	9.4 (0.9)	5.6 (0.5)	10.5 (0.8)	7.2 (0.8)	12.2 (1.1)	6.8 (0.7)	12.7 (1.1)
VC SBP (%)	PLA	6.6 (0.8)	5.4 (0.6)	6.0 (0.6)	5.0 (0.5)	5.6 (0.5)	4.6 (0.5)	5.7 (0.6)	4.2 (0.5)	5.3 (0.5)	4.4 (0.6)	5.2 (0.6)
	LOR	6.3 (0.5)	4.1 (0.4)	6.3 (0.7)	4.7 (0.5)	5.9 (0.6)	4.2 (0.4)	5.6 (0.5)	3.9 (0.4)	6.0 (0.5)	4.6 (0.4)	5.8 (0.6)
VC DBP (%)	PLA	6.3 (0.7)	4.9 (0.6)	6.6 (0.7)	4.7 (0.4)	6.7 (0.9)	5.0 (0.7)	7.1 (0.9)	5.5 (0.9)	7.1 (1.0)	5.2 (0.6)	7.5 (1.1)
	LOR	6.5 (0.7)	4.8 (0.3)	6.6 (0.7)	5.0 (0.3)	6.8 (0.7)	4.7 (0.3)	6.9 (0.5)	4.9 (0.4)	7.3 (0.6)	5.9 (0.6)	7.7 (0.8)
DBP (mmHg)	PLA	59 (4)	72 (5)	61 (4)	70 (4)	63 (4)	70 (4)	65 (4)	70 (4)	70 (5)	72 (5)	67 (4)
	LOR	60 (6)	75 (7)	62 (4)	70 (4)	64 (5)	71 (5)	65 (4)	73 (4)	68 (4)	76 (4)	69 (4)
LFB DBP	PLA	7.3 (0.2)	6.4 (0.2)	7.2 (0.3)	6.6 (0.2)	7.4 (0.3)	6.6 (0.3)	7.5 (0.3)	6.6 (0.4)	7.4 (0.3)	6.8 (0.2)	7.7 (0.3)
	LOR	7.3 (0.3)	6.4 (0.2)	7.3 (0.2)	6.6 (0.1)	7.4 (0.2)	6.6 (0.2)	7.6 (0.2)	6.7 (0.2)	7.8 (0.1)	6.9 (0.2)	7.9 (0.2)
MFB DBP	PLA	6.5 (0.3)	5.9 (0.3)	6.7 (0.3)	6.1 (0.2)	6.8 (0.3)	6.3 (0.3)	6.6 (0.3)	6.2 (0.3)	6.6 (0.4)	6.1 (0.2)	6.7 (0.2)
	LOR	6.7 (0.3)	6.2 (0.2)	6.8 (0.2)	6.2 (0.2)	6.7 (0.3)	6.2 (0.2)	6.7 (0.3)	6.3 (0.3)	6.8 (0.3)	6.2 (0.2)	6.9 (0.2)
HFB DBP	PLA	5.2 (0.1)	5.1 (0.3)	5.7 (0.3)	5.0 (0.2)	5.6 (0.3)	5.0 (0.3)	5.5 (0.3)	5.1 (0.4)	5.3 (0.3)	5.3 (0.3)	5.7 (0.3)
	LOR	5.5 (0.4)	5.0 (0.1)	5.5 (0.3)	5.1 (0.2)	5.6 (0.3)	4.9 (0.2)	5.7 (0.2)	5.1 (0.2)	5.8 (0.3)	5.2 (0.2)	5.9 (0.2)

Discussion

Although a limited number of subjects ($n = 9$) were incorporated in this study an interesting aspect of the mechanism of action of lorazepam was revealed by our data, indicating a specific parasympathetic effect after low doses of this benzodiazepine.

Cardiovascular variability during rest

Previously, we suggested that the observed decrease in HR might indicate a stimulating effect of LOR on cardiac vagal tone during rest (Tulen et al. 1991). The present dose-dependent increases in BRS, and LFB, MFB, and HFB power of HR and the absence of changes in BP variability lend direct support to this hypothesis. It has been shown that high, mid and low frequency fluctuations in HR can be influenced by parasympathetic mechanisms during situations of rest (Akselrod et al. 1985; Pomeranz et al. 1985) and the increase in BRS may also be the result of parasympathetic stimulation (Eckberg et al. 1971).

Adinoff et al. (1992) reported an opposite effect in a similar, although not placebo-controlled, research protocol in healthy subjects after intravenous administration of diazepam: a dose-dependent increase in HR and a dose-dependent attenuation of cardiac vagal tone. Although their and our data underline an effect of benzodiazepines on cardiac vagal tone, the direction of the effect clearly is not similar for all benzodiazepines. In our design, we additionally used repeated presentations of the CWT between the rest periods: it cannot be excluded that rebound phenomena due to the strain of the tasks influenced the responses during periods of rest. However, pharmacokinetic differences between diazepam and lorazepam may be more relevant for the interpretation of these experiments. We have chosen lorazepam because it has a short distribution half-life and no active metabolites, which in combination with an elimination half-life of 12–13 h makes cumulative dose administration possible. This assumption is supported by our pharmacokinetic data (Table 1). Diazepam, on the other hand, is much more lipophilic, which will result in high brain concentrations immediately after intravenous administration and a swift decrease within minutes. In mice, for example it has been shown that diazepam concentration in the brain is reduced tenfold between 10 and 30 min after intravenous administration, whereas lorazepam concentrations were rather constant during the first hour after administration (Greenblatt and Sethy 1990). Adinoff et al. (1992) do not present plasma data of diazepam and its active metabolites, nor do they present data on respiratory or sedative effects of diazepam, which could explain the effects on vagal tone. However, the opposite results obtained with diazepam and lorazepam can only be clarified when both drugs are compared within the same experiment. Opposite effects on cardiac vagal activity of two different GABA-ergic systems have been described (Wible and DiMicco 1986) and, although benzodiazepines may not necessarily be

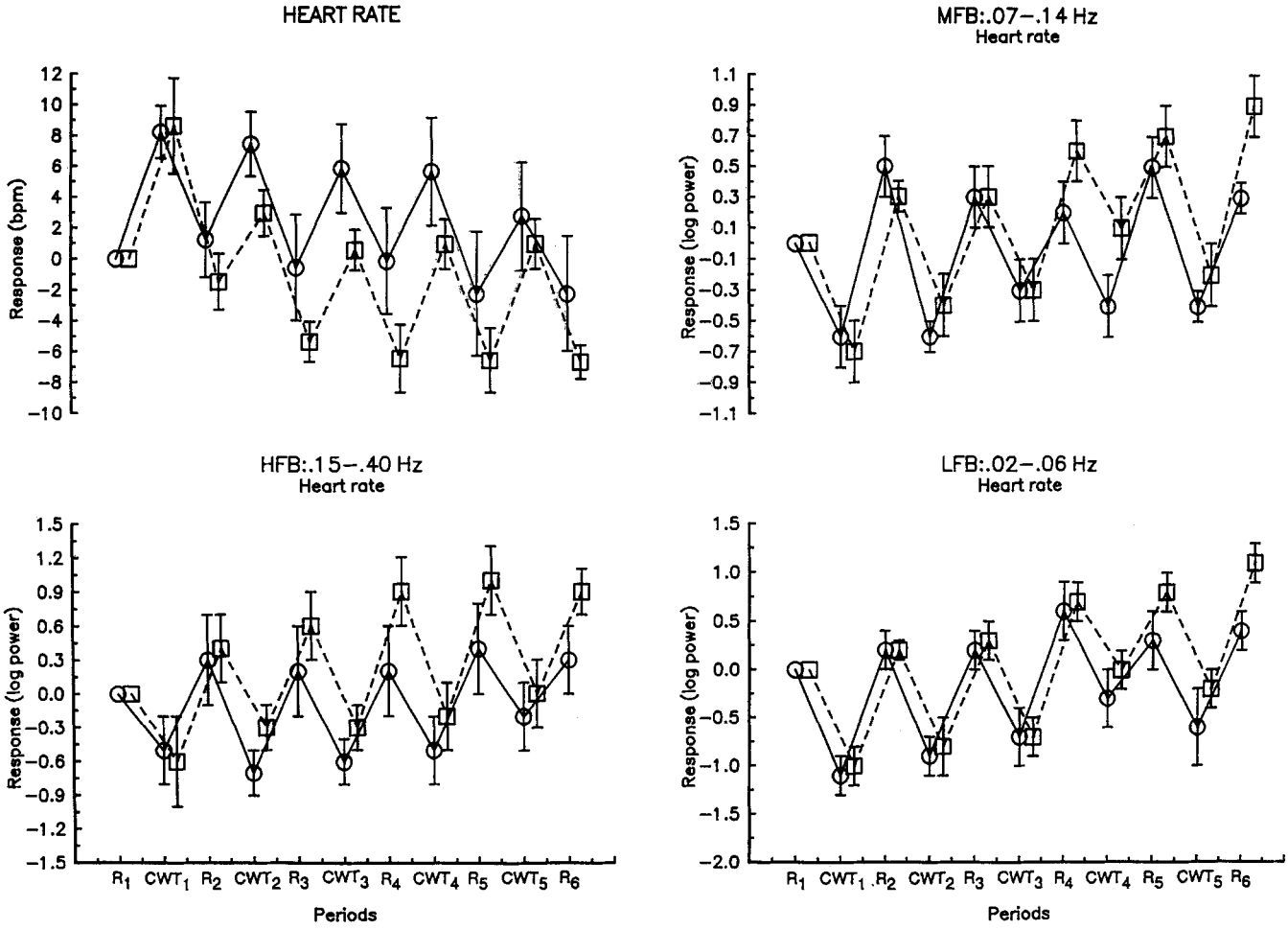

Fig. 1. Mean (±SEM) values of HR and HFB, MFB, and LFB log power of HR, during the consecutive periods of rest and CWT. ○, placebo; □, lorazepam

involved, similar opposite mechanisms cannot be excluded for benzodiazepines.

The observed increase in vagal tone induced by LOR could be caused by respiratory effects. Benzodiazepines are known to cause respiratory depression, especially after intravenous administration of high doses (Danneberg 1986; Berggren et al. 1987). Regarding LOR, a lack of respiratory effects (Gasser et al. 1975; Elliott et al. 1971), respiratory stimulation (Paulson et al. 1983; Dodson et al. 1976), or respiratory inhibition (Wettstein et al. 1990) have been reported. In this study with low doses, LOR did not induce clear respiratory effects on the parameters measured, indicating that the cardiac effects cannot be explained by changes in respiration.

Sedative effects of lorazepam, mediated by suppression of locus coeruleus firing (Grant et al. 1980) might also explain the observed effects on HR, BRS and HR fluctuations. Previously, we have shown that after the highest cumulative dose (0.94 mg), LOR induced significant sedative effects as indicated by performance impairment, increased fatigue and decreased vigor (Tulen et al. 1991). After the highest dose plasma noradrenaline concentrations were also lowered in comparison with the PLA session, reflecting a suppression of sympathetic nervous system activity, but only after the highest dose of LOR. HR, HFB fluctuations and BRS already changed significantly after 0.44 mg LOR; MFB and LFB fluctuations changed significantly after 0.94 mg LOR. Thus, the effects of LOR at the lower doses do not appear to be related to sedation.

Overall, the present data indicate a stimulating effect of LOR on cardiac parasympathetic activity during periods of rest.

Cardiovascular variability to the Stroop Color Word Test (CWT)

The CWT significantly increased HR, SBP, DBP and respiration rate and significantly decreased BRS, respiratory depth and LFB and MFB fluctuations in HR, SBP and DBP as well as HFB fluctuations in HR and DBP. LOR did not induce clear effects on the variability responses to the CWT. The SBP and DBP response magnitudes to the CWTs showed a habituation effect during both sessions; the other parameters showed similar response magnitudes to the five consecutive CWTs. Our results of decreased HR and BP variability in the three frequency bands during a mental task correspond with findings of others (Mulder and Mulder 1981;

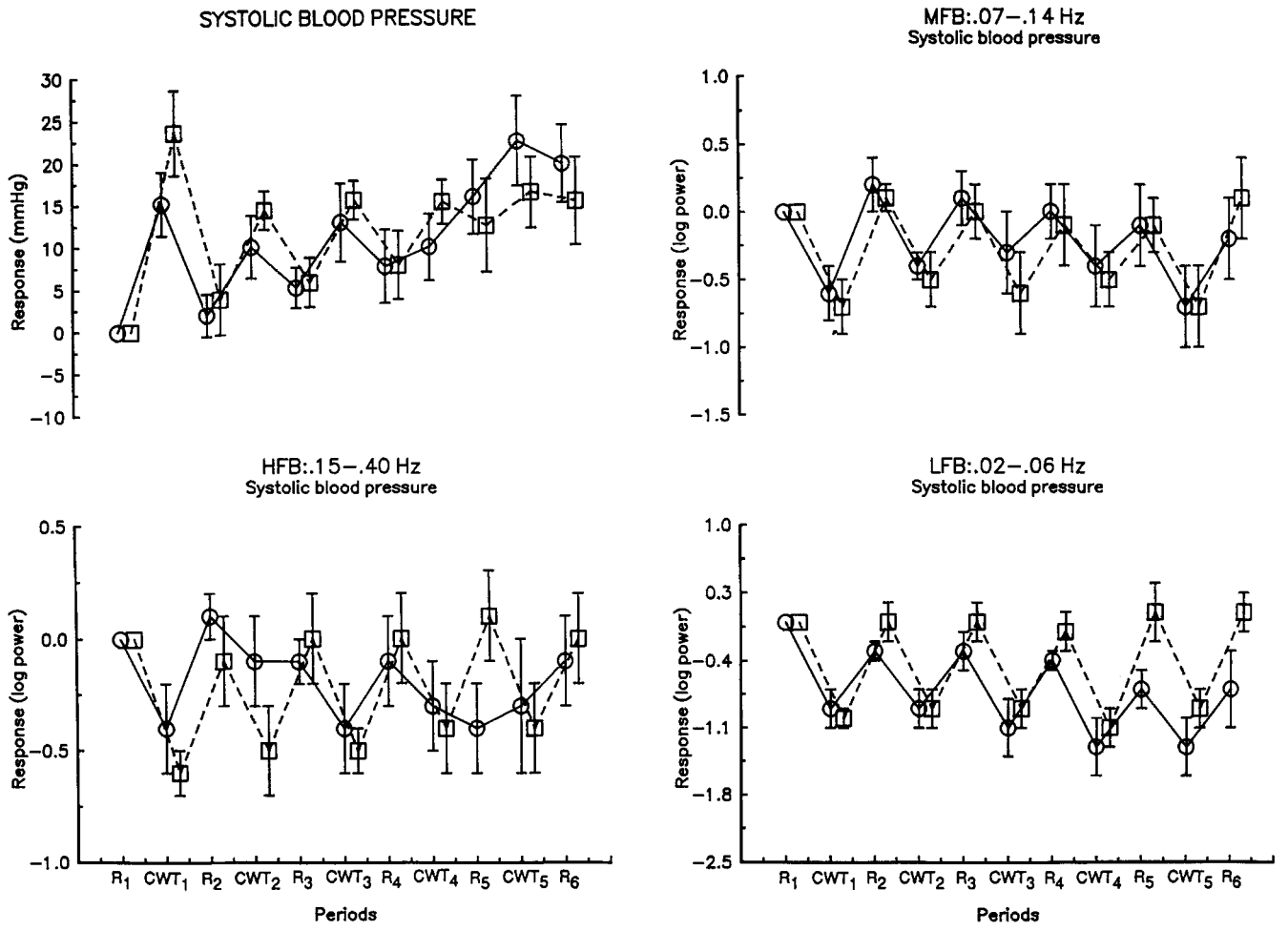

Fig. 2. Mean (±SEM) values of SBP and HFB, MFB and LFB log power of SBP, during the consecutive periods of rest and CWT. ○, placebo; □, lorazepam

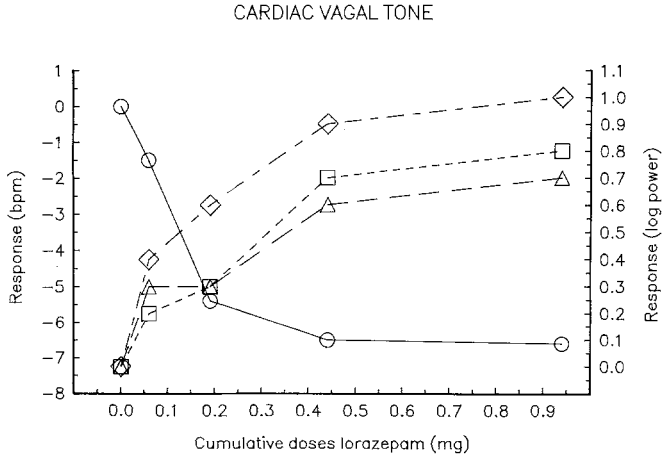

Fig. 3. Dose-response effects of changes in HR and changes in LFB, MFB and HFB power of HR, after intravenous administration of lorazepam. ○, heart rate; □ LFB; △ MFB; ◇ HFB

Veldman et al. 1985; Langewitz and Rüddel 1989). Similarly, a reduction in BRS during psychological stress has been observed in a number of studies, in which BRS during mental stress was computed either after application of a pressor agent (Sleight et al. 1978; Conway et al. 1983), the neck suction method (Ditto and France 1990), or by means of non-invasive methods (Robbe et al. 1987; Steptoe and Sawada 1989; Pagani et al. 1991). Overall, the reduced variability in HR and BP during the CWT resembles a pattern of a parasympathetic withdrawal (Akselrod et al. 1985; Pomeranz et al. 1985). However, previously we have established that the CWT induces a defence-like reaction by means of sympatho-adrenomedullary activation; the CWT increased HR, plasma and urinary adrenaline, electrodermal activity and muscular tension, whereas it decreased finger pulse amplitude (Tulen et al. 1989). The present study does not permit differentiation between parasympathetic withdrawal, sympathetic activation, or both, as a possible cause for the changes in cardiovascular variability observed during the CWT. It is clear, however, that LOR had no effect on these cardiovascular responses to the CWT, although performance of the task deteriorated severely after the highest dose (0.94 mg LOR), apparently due to the sedative effects of LOR (Tulen et al. 1991).

In conclusion, in this study, we observed a specific effect of LOR on parasympathetic activity: LOR induced dose-dependent increases in cardiac vagal tone. This effect

Table 4. Mean (SEM) values of BRS and respiratory cycle duration, respiratory depth and the number of sighs and hypopnoeas, during the consecutive periods of rest and CWT, for the placebo (*PLA*) and lorazepam (*LOR*) sessions separately

		Rest1	CWT1	Rest2	CWT2	Rest3	CWT3	Rest4	CWT4	Rest5	CWT5	Rest6
BRS (msec/mmHg)	PLA	15 (2)	12 (3)	16 (2)	10 (2)	15 (1)	12 (1)	15 (1)	12 (2)	19 (3)	13 (2)	16 (2)
	LOR	11 (2)	8 (1)	13 (2)	11 (1)	13 (2)	11 (1)	16 (2)	12 (1)	17 (2)	13 (2)	19 (3)
Resp. cycle (sec)	PLA	4.1 (0.4)	3.1 (0.2)	4.3 (0.4)	3.2 (0.2)	4.0 (0.2)	3.2 (0.2)	4.0 (0.2)	3.3 (0.2)	4.3 (0.4)	3.2 (0.2)	4.2 (0.4)
	LOR	3.9 (0.2)	2.9 (0.1)	3.9 (0.3)	3.2 (0.2)	3.7 (0.2)	3.1 (0.2)	3.8 (0.2)	3.1 (0.2)	3.9 (0.2)	3.1 (0.2)	3.6 (0.2)
Resp. depth (% baseline)	PLA	100 (0)	91 (4)	104 (3)	92 (6)	100 (4)	89 (4)	97 (3)	94 (7)	94 (7)	87 (4)	96 (4)
	LOR	100 (0)	88 (5)	103 (6)	90 (5)	99 (5)	89 (6)	99 (4)	90 (6)	98 (4)	91 (7)	95 (6)
Sighs (*n*)	PLA	3.4 (1.0)	3.0 (1.0)	5.7 (1.3)	4.0 (0.6)	5.9 (1.6)	3.3 (0.7)	5.1 (1.1)	4.2 (0.8)	5.2 (1.2)	1.9 (0.3)	4.8 (1.1)
	LOR	3.7 (0.7)	2.8 (0.7)	3.9 (0.9)	3.3 (0.6)	4.3 (1.3)	3.6 (0.7)	4.7 (1.6)	5.1 (0.9)	6.8 (1.8)	4.3 (0.5)	5.9 (1.9)
Hypopnoeas (*n*)	PLA	5.3 (2.6)	3.7 (0.9)	2.6 (0.9)	4.7 (1.8)	4.4 (1.3)	4.8 (1.3)	4.0 (1.7)	3.2 (1.0)	2.6 (0.9)	4.9 (1.4)	3.2 (1.5)
	LOR	3.7 (1.5)	4.3 (1.4)	3.4 (0.5)	3.6 (0.6)	3.0 (0.9)	3.2 (1.2)	3.0 (1.3)	5.3 (0.9)	4.8 (1.2)	4.6 (1.0)	7.6 (4.1)

of LOR was apparent only during periods of rest and, at low doses, appeared not to be related to diminished sympathetic activity, altered respiration, or increased sedation. These data show that spectral analysis of beat to beat fluctuations in HR and BP represents a useful tool to elucidate sympathetic and parasympathetic activity within cardiovascular control mechanisms after benzodiazepine administration. This approach is valuable for our insight into the effects of benzodiazepines on autonomic nervous system activity during various situations of rest or stress and anxiety.

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