Power spectrum analysis of heart rate variability in Guillain–Barré syndrome
A longitudinal study

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Summary
Power spectrum analysis of heart rate variability was repeatedly carried out on 13 patients with Guillain–Barré syndrome for up to 1 year by Fourier analysis of regular beat-to-beat (R–R) intervals which were recorded for 5 min, converted into a continuous function by linear interpolation and resampled at 5 Hz. Low-frequency (LF) power (reflecting a mixture of parasympathetic and sympathetic activity) and high-frequency (HF) power (reflecting parasympathetic tone) were calculated by integrating the spectra from 0.04 to 0.15 Hz and from 0.15 to 0.4 Hz, respectively. At the height of the disease, the HF component was significantly decreased. The LF : HF ratio, which has been suggested to be an indicator for sympathetic activity, was increased compared with the follow-up value after 1 year. Both measures returned to normal gradually over time. Pooled-data analysis suggested that both HF and LF power were significantly related to the responses of standardized parasympathetic function tests, while the LF : HF ratio was inversely correlated with sympathetic vasomotor activity. In patients presenting with tachycardia, LF and HF power were strikingly decreased compared with patients with normal heart rates, while in patients showing vagal over-reactivity, the power of both spectral bands was significantly increased. The results suggest that spectral analysis of heart rate variability is useful for investigating the cardiovascular neural regulation in patients with Guillain–Barré syndrome. In this disorder, the sympathovagal balance is clearly shifted to sympathetic predominance at the height of the disease.

Keywords: Guillain–Barré syndrome; power spectrum analysis; autonomic dysfunction; vagal nerve; tachycardia

Abbreviations: HF = high-frequency (power); HRACP = heart rate response to active change of posture; I–E = heart rate response to deep inspiration–expiration; LF = low-frequency (power); PSA = power spectrum analysis; VR = heart rate response to the Valsalva manoeuvre

Introduction
Power spectrum analysis (PSA) of heart rate variability is a useful non-invasive technique to investigate the neural mechanisms underlying cardiovascular regulation in the frequency domain (Akselrod et al., 1981, 1985; Pomeranz et al., 1985; Pagani et al., 1986). The two main regions of interest are a low-frequency (LF) component between 0.04 and 0.15 Hz which is influenced by both the sympathetic and parasympathetic nervous system (Akselrod et al., 1981; Pomeranz et al., 1985), and a high-frequency (HF) component mainly reflecting cardiovagal tone (Akselrod et al., 1981; Pomeranz et al., 1985; Pagani et al., 1986). The ratio of the power at low- and high-frequencies (LF : HF) has been suggested to be an indicator of sympathetic nervous system activity (Akselrod et al., 1985; Pagani et al., 1986). HF and LF power were highly related to the measures of heart rate variability estimated in the time domain (Bigger et al., 1992), whereas correlation analysis of power spectra and standardized tests of autonomic function in healthy volunteers (Sega et al., 1993) and in patients with diabetic neuropathy (Freeman et al., 1991) yielded conflicting results.

Autonomic neuropathy is a common and important complication in the Guillain–Barré syndrome, and it can affect cardiovascular, sudomotor, gastrointestinal and other systems involving both parasympathetic and sympathetic fibres (Hughes, 1990; Arnason and Soliven, 1993; Zochodne, 1994). Serious cardiovascular dysfunction may present as...
sustained or episodic hypertension, pronounced blood pressure fluctuation, orthostatic hypotension, sinus tachycardia or serious bradyarrhythmia (Hund et al., 1994, 1993; Ropper, 1994; Flachenecker et al., 1996). Recently, we have described the time course of autonomic dysfunction assessed by standardized autonomic tests in a cohort of patients with Guillain–Barré syndrome followed prospectively for 1 year (Flachenecker et al., 1997). However, a significant proportion of these patients could not be evaluated properly during the height of the disease, due to severe disability that interfered with the execution of the test procedures. In contrast, PSA may be easily administered but, to date, it has not been studied systematically in patients with Guillain–Barré syndrome.

Therefore, the objectives of this study were to assess parasympathetic and sympathetic activity in patients with Guillain–Barré syndrome by means of PSA, and to correlate these measures with those obtained in the time domain and with standardized autonomic function tests. We also studied the relation between these findings and clinically overt autonomic dysfunction.

**Subjects and methods**

**Patients**

The detailed characteristics of patient recruitment were as described previously (Flachenecker et al., 1996, 1997). Briefly, all the patients enrolled in our department in the multicentre controlled Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Study (Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group, 1997) between July 1993 and March 1995 were also recruited for this study. In addition, one patient with milder disability than required for inclusion in the therapeutic trial was also accepted as was one patient who had previously been treated with intravenous immunoglobulins.

Thus, 13 patients with Guillain–Barré syndrome (six females, seven males) were included for PSA. The mean age of these patients was 52.5 years (range 29–70, median 56 years). The mean duration (± SD) of the progressive phase was 7.0 ± 3.2 days (range 4–14, median 5 days) and of the plateau phase, 5.2 ± 7.5 days (range 1–28, median 2 days). Three out of 13 patients (23%) required mechanical ventilation for 7–30 days. None died during the study period. The most frequent pre-existing disease was arterial hypertension in five patients; other concomitant conditions included chronic obstructive pulmonary disease (n = 1), thyroiditis (n = 1), heart failure (n = 1), diabetes mellitus (n = 1) and chronic alcohol abuse (n = 1).

In accordance with the Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Study protocol, three patients (23%) were randomized to treatment with plasma exchange, three (23%) to intravenous immunoglobulins, and five (39%) to a combination of both. Two patients (15%) received no specific therapy. Symptomatic treatment included heparin, antacids, mucolytics (i.e. acetylcysteine), antibiotics, analgesics, narcotics, and sedating and antihypertensive agents, and it was allowed at the discretion of the treating physician. A detailed description of these medication regimes is given elsewhere (Flachenecker et al., 1997).

**Control subjects**

The age-matched control group consisted of 13 patients with other neurological diseases who were examined once, 10 males, three females, aged 50.0 ± 15.0 years (range 24–72, median 52 years) without any signs and symptoms of autonomic dysfunction, and without medication known to affect the autonomic nervous system. These patients suffered from cerebrovascular disorders (n = 5), epileptic seizures (n = 3), inflammatory CNS disorders (n = 2) or radicular pain syndromes (n = 3). Informed consent was obtained from all patients and control subjects, and the study was approved by the Ethics Committee of the Julius-Maximilians-Universität Würzburg, Germany.

**PSA**

PSA was obtained after 15-min rest in a lying position with a 30° head-up tilt. Apart from patients requiring mechanical ventilation, the subjects were awake, without distress and breathing quietly. The electrocardiogram was recorded continuously for 5 min using three chest electrodes corresponding to lead II and amplified by a Servomed recording system (Hellige, Freiburg, Germany). The signal was digitized on-line (12 bit A/D-board DT 2812, Data-Translation, Marlboro, Mass., USA) at a rate of 1000 Hz and stored on hard disk. Each QRS complex was recognized using an autocorrelation algorithm with visual check. From this, beat-to-beat (R–R) intervals were automatically detected with an accuracy of 1 ms, thus constituting the tachogram (Fig. 1) which was converted into a continuous function by linear interpolation and resampled at 5 Hz resulting in data sets of 1500 points each (Karemaker, 1993; Pieper and Hammill, 1995). Singular extrasystoles were also interpolated, while data sets with frequent premature beats (>15% of R–R intervals) were excluded from further analysis (Pieper and Hammill, 1995). The spectral components were obtained by harmonic Fourier analysis in the 0.0033–0.5 Hz frequency range, with the power reflecting the square of the amplitudes (Luczak and Lurag, 1973). LF and HF power were calculated by integrating the spectra over the 0.04–0.15 Hz and 0.15–0.40 Hz ranges, respectively (Bigger et al., 1992), and corrected for the square of the mean heart rate (Baharav et al., 1995). Thus, the resulting power was unitless.

Systolic and diastolic blood pressures were measured with a sphygmomanometer and automatically recorded at intervals of 1 min each (Critikon Dinamap monitor, Johnson and Johnson, Norderstedt, Germany).
Power spectrum analysis in Guillain–Barre syndrome

Fig. 1 Power spectrum analysis in a single patient with Guillain–Barre syndrome. R–R intervals throughout a 5-min epoch at the height of the disease (A) and after 1 year (B), are plotted against the number of consecutive R–R intervals constituting the tachogram (left). From this, the power spectrum density (PSD) at each frequency is derived, with the integrals from 0.04 to 0.15 Hz reflecting low-frequency (LF) power, and from 0.15 to 0.4 Hz high-frequency (HF) power (right). Note the nearly complete absence of the HF component in acute Guillain–Barre syndrome (A), which had reappeared after 1 year (B, right) as reflected by a broader band-width of the tachogram (B, left).

Longitudinal study of PSA
The power spectrum was obtained immediately after admission and repeated at least on days 1, 2, 4 and 7, during weeks 2, 4, 12 and 24, as well as at the 1 year follow-up. In order to exclude major circadian variations, the procedure was always done between 9.00 a.m. and 2.00 p.m.

Autonomic dysfunction
Autonomic dysfunction was evaluated by standardized tests of cardiogal function, i.e. heart rate responses to the Valsalva manoeuvre (VR), deep breathing with the inspiration–expiration difference (I–E) and active change of posture HRACP, and sympathetic vasomotor activity (blood pressure responses to active change of posture and to sustained handgrip) (Flachenecker et al., 1997; Therapeutics and Technology Assessment Subcommittee, 1996). These tests were done each time the power spectrum was studied. Out of these, a 10-point composite autonomic score, and subscores for parasympathetic and sympathetic dysfunction, were obtained as described previously, with higher scores indicating more severe autonomic failure (Flachenecker et al., 1997). The parameters of heart rate variability derived in the time domain comprised the standard deviation of all normal R–R intervals, the root-mean-square successive difference, and the percentage of differences between adjacent normal R–R intervals that are >50 ms for the whole 5-min epoch (Bigger et al., 1992). The clinical signs of autonomic dysfunction considered were (i) tachycardia, defined as heart rate of >100 b.p.m.; and (ii) abnormal sensitivity to eyeball pressure testing, defined as a decrease of heart rate to <40 b.p.m. (Flachenecker et al., 1996), in the absence of fever, hypovolemia, hypoxemia, psychotic states or autonically active medication. The disease stages were divided into progressive, plateau and remission phase by clinical criteria. The remission phase was further subdivided into early (within 7 days of improvement), middle (7–28 days after start of recovery) and late remission phase (>28 days after the first signs of improvement). In cases where two or more observations fell within one phase, the first measurement within the above mentioned boundaries was chosen as representative for the disease stage. Thus, only single values were used for time-course and correlation analysis. Most baseline measurements fell into the progressive phase; in three patients, the first evaluation took place during the plateau phase.

Statistics
Non-parametric tests were used for all comparisons. Differences between disease stages were analysed by the
Wilcoxon signed rank sum test, and different patient groups were compared with the Mann–Whitney rank sum test. Correlation coefficients were calculated by Spearman rank order correlation (standard software package SIGMAStat for Windows Version 1.0, Jandel Corporation, San Rafael, Calif., USA). Results were considered statistically significant if $P < 0.05$.

**Results**

**PSA**

During the study period, a total of 164 PSAs were done in 13 patients with Guillain–Barré syndrome (range 7–21, median 13 per patient). One patient was lost to follow-up. Seven recordings (4.3%) were rejected because of frequent premature beats. Of the remaining analyses, 131 (79.9%) showed no extrasystoles at all, whereas 17 (10.4%) exhibited <1% premature beats, five (3.0%) between 1% and 3% and four (2.4%) between 3% and 13%. The power spectrum of one patient at the height of the disease, and after 1 year, is illustrated in Fig. 1. There was an increase in LF power ($1.1 \times 10^5$ versus $0.5 \times 10^5$), and a marked reduction of HF power ($1.0 \times 10^4$ versus $4.0 \times 10^4$) at the plateau phase (Fig. 1A) compared with follow-up after 1 year (Fig. 1B). Consequently, the LF : HF ratio dropped from 10.9 at plateau to 1.2 after 1 year.

The group analysis of the time courses of LF, HF and the LF : HF ratio is depicted in Fig. 2. The HF power was reduced during the acute stages of the disease, with a subsequent recovery to values equaling those of patients with other neurological diseases (Fig. 2B and Table 1), whereas LF power was rather unchanged during the entire study period (Fig. 2A). The time course of the LF : HF ratio was inversely related to that of HF power (Fig. 2C). The decrease of HF power at the height of the disease (early and middle remission phase) was statistically significant compared with the follow-up at 1 year, and with data from patients with other neurological diseases ($P < 0.005$), whilst the increase in the LF : HF ratio only showed significance compared with other neurological diseases ($P < 0.03$). However, there was a trend for higher LF : HF ratios in the early remission phase compared with the follow-up at 1 year ($P = 0.052$). The LF power was not different between disease stages or between patients with Guillain–Barré syndrome and other neurological diseases (Table 1).

These findings were confirmed by the individual changes in PSA parameters (Fig. 3). The HF power was consistently enhanced at the follow-up at 1 year compared with the early remission phase in 11 patients and only slightly decreased in one patient (Fig. 3B). Similarly, the LF : HF ratio was decreased in 10 patients and increased in only two patients at follow-up (Fig. 3C). The changes in LF power were far more inconsistent with higher values at the 1 year follow-up in eight patients, and lower values in three patients; one patient had similar values at the early remission phase and after 1 year (Fig. 3A).

![Fig. 2 Time course of spectral parameters in 13 patients with Guillain–Barré syndrome. Box-and-whisker plots of low-frequency (LF) power (0.04–0.15 Hz) (A), high-frequency (HF) power (0.15–0.4 Hz) (B) and the LF : HF ratio (C) according to disease stages (n = 13). Boxes, 25–75% quartiles; whiskers, 10–90% percentiles; solid lines, median values; open circles, single values outside the 10% and 90% percentiles. Base = baseline (first acute stage) evaluation; PLP = plateau phase; RMPe = early remission phase (within 7 days of remission onset); RMPm = remission phase 7–28 days after onset of recovery; RPMl = late remission phase, i.e. >28 days after onset of recovery; End = follow-up after 1 year. *$P < 0.05$ compared with End (Wilcoxon signed rank sum test).](image-url)
Table 1  Power spectrum analysis in patients with Guillain–Barré syndrome and other neurological diseases

<table>
<thead>
<tr>
<th></th>
<th>Guillain–Barré syndrome (n = 13)</th>
<th>At the 1 year follow-up (n = 12)</th>
<th>Other neurological diseases (n = 13)</th>
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<tr>
<td>Age in years</td>
<td>56 (51–57)</td>
<td>57 (52–58)</td>
<td>52 (37–64)</td>
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<tr>
<td>LF power (×10^5)</td>
<td>0.4 (0.2–1.7)</td>
<td>0.8 (0.6–1.7)</td>
<td>1.2 (0.7–2.0)</td>
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<tr>
<td>HF power (×10^5)</td>
<td>0.1 (0.0–0.2)***</td>
<td>0.3 (0.2–0.5)</td>
<td>0.4 (0.2–0.8)</td>
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<tr>
<td>LF : HF power ratio</td>
<td>7.8 (3.7–13.5)*</td>
<td>4.0 (2.2–7.1)</td>
<td>3.2 (1.4–5.2)</td>
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†Data are expressed as medians, the numbers in brackets represent 25–75% quartiles. ‡Within 7 days of start of recovery. LF = low-frequency (0.04–0.15 Hz); HF = high-frequency (0.15–0.40 Hz). ***P < 0.005, early remission phase compared with follow-up at 1 year (Wilcoxon signed rank sum test) and other neurological diseases (Mann–Whitney rank sum test). *P < 0.05, early remission phase compared with other neurological diseases (Mann–Whitney rank sum test).

Influence of medication and mechanical ventilation
Symptomatic treatment comprised narcotics, sedatives, analgesics, catecholamines and antihypertensive agents, and was mainly administered to patients requiring mechanical ventilation or to patients with preexisting arterial hypertension. In these patients, antihypertensive treatment was essentially unchanged during the whole study period. Five patients received none of these drugs. There were no substantial differences in the time courses of the spectral parameters in patients with and without additional medication, or in those requiring mechanical ventilation (Fig. 3). Moreover, subgroup analysis of six patients receiving no autonomically active medication, or unchanged medication during the study period revealed results essentially similar to those in the whole study group, with a median HF power of 2.0×10^4 versus 4.8×10^4, and a median LF : HF ratio of 11.0 versus 3.2 (early remission phase compared with the 1 year follow-up). Also, the time courses of LF, HF and the LF : HF ratio in the 10 patients without mechanical ventilation were similar to those of the whole study group (data not shown).

Correlation of PSA, autonomic function tests and time domain measures
Both LF and HF power were significantly correlated with cardiovagal reflex tests (VR, I–E and HRACP), while there was only an inconsistent association between HF power and sympathetic vasomotor activity (blood pressure responses to active change of posture and sustained handgrip) (Table 2). HF power was negatively associated with all composite dysfunction scores (composite autonomic score, parasympathetic score and sympathetic score), whereas LF power was not related to the sympathetic score. Surprisingly, the LF : HF ratio was inversely related to sympathetic vasomotor function (blood pressure responses to active change of posture and sustained handgrip), with only a weak relationship to one of the cardiovagal function tests (VR). The sympathetic dysfunction score was the only composite score correlated with the LF : HF ratio (Table 2). The measures of the time domain were also strongly correlated with both LF and HF components, while the LF : HF ratio was not related to any of these parameters (Table 3). As theoretically expected, total spectral power was almost perfectly correlated with the standard deviation of all normal R–R intervals (r = 0.93).

PSA and clinical autonomic dysfunction
In patients with tachycardia, both LF and HF power were significantly decreased compared with patients with normal heart rates, with these changes being more pronounced for the LF component (Fig. 4A and B) whereas the LF : HF ratio was not different between the groups (Fig. 4C). This holds also true for patients with and without mechanical ventilation (data not shown). In contrast, in patients with abnormal sensitivity to eyeball pressure testing, i.e. those with vagal over-reactivity, LF and HF power were increased compared with patients with normal responses (Fig. 4A and B). Again, the LF : HF ratio was essentially similar in both autonomic states (Fig. 4C).

Discussion
This study shows that PSA of heart rate variability is useful in assessing the cardiovascular neural regulation in patients with Guillain–Barré syndrome. In early stages of the disease, the sympatho-vagal balance was clearly shifted to sympathetic predominance. LF and HF components were closely correlated with the responses of cardiovagal reflex tests, whereas the LF : HF ratio as a marker of sympathetic activity was inversely related to sympathetic vasomotor function. PSA may thus provide insight into the mechanisms involved in clinically relevant autonomic dysfunction.

Spectral analysis of heart rate variability has been increasingly used as a clinical test of autonomic nervous system function and has been shown to provide a reliable...
Fig. 3 Individual results of power spectrum analysis in 13 patients with Guillain–Barre syndrome. Low-frequency (LF) power (0.04–0.15 Hz) (A), high-frequency (HF) power (0.15–0.4 Hz) (B) and the LF : HF ratio (C) at the early remission phase (RMpe) and after 1 year (End). Each symbol represents one patient and one observation. Left: patients without medication. Right: patients requiring mechanical ventilation (open symbols) or additional medication (closed symbols).

A quantitative estimate of the cardiovascular neural regulation (Akselrod et al., 1981; Pomeranz et al., 1985; Pagani et al., 1986; Spiers et al., 1993). However, different techniques of analysis and different frequency bands were used by the different authors (Spiers et al., 1993). In an attempt to correlate time- and frequency-domain measures, Bigger et al. (1992) defined the energy of the power spectrum between 0.04 and 0.15 Hz as LF power, and the energy between 0.15 and 0.4 Hz as HF power. By using these definitions, we found a rather similar correlation between LF and HF power, and between the measures obtained in the frequency and time domain (Table 3). This provides further evidence that the standard deviation of all normal R–R intervals is mainly related to LF power, and that the root-mean-square successive difference, like the percentage of differences between adjacent normal R–R intervals that are >50 ms, is mainly related to HF power. These estimates measure sudden changes in heart rate reflecting parasympathetic activity which could modulate the heart rate on a beat-to-beat basis (Bigger et al., 1988; Spiers et al., 1993). As in the study of Bigger et al. (1992), the LF : HF ratio was not correlated with any of the time-domain measures, indicating that the measures in the frequency domain may provide complementary information about the cardiovascular neural regulation. As expected from theoretical considerations, the correlation of total spectral power with the standard deviation of all normal R–R intervals was very strong (r ~ 1) indicating that the pre-processing of the data and the calculations of the Fourier transformation did not distort the results (Bigger et al., 1992). Thus, the spectral parameters obtained in our study were a reliable estimate of the power spectrum of heart rate variability.

The physiological interpretation of the spectral data is still a matter of debate (Karemaker, 1993). Studies using pharmacological blockade and physiological stimuli have demonstrated that the HF component reflecting respiratory sinus arrhythmia was mediated solely by the parasympathetic nervous system, and was depressed in the upright position (Akselrod et al., 1981, 1985; Pomeranz et al., 1985; Linden and Diehl, 1996); for these oscillations, a baroreflex contribution is likely (Karemaker, 1993). The low-frequency power, with its relationship to the respiratory cycle, is commonly associated with respiratory sinus arrhythmia and has been used as an index of cardiac vagal tone. The LF component, on the other hand, is linked to the heart rate variability, and has been shown to reflect both neural and sympathetic activity.
component which is augmented in the standing position has been suggested to reflect a mixture of cardiac parasympathetic and sympathetic tone (Akselrod et al., 1981; Pomeranz et al., 1985; Pagani et al., 1986; Linden and Diehl, 1996). This frequency band was thought to represent baroreflex-mediated heart-rate changes induced by oscillations of the arterial blood pressure in the same frequency range (the so-called ‘Mayer waves’), which were related to fluctuations in peripheral vascular tone (Karemaker, 1993; van Ravenswaaij Arts et al., 1993). The LF : HF ratio has been suggested to be an indicator of cardiac sympathetic activity (Pagani et al., 1986; Ewing, 1992). The covariance of spectral parameters and standardized autonomic tests in our study generally support the considerations detailed above: the responses to cardiovasal reflex tests were significantly correlated with both LF and HF power, as has been previously reported in patients with diabetic autonomic neuropathy (Freeman et al., 1991) and in healthy volunteers (Sega et al., 1993; Linden and Diehl, 1996); these associations were more pronounced for the HF band. Examination of the relationship of the VR following the Valsalva manoeuvre to both spectral parameters in 13 Guillain–Barré syndrome patients, each studied during six disease stages. The numbers in brackets denote the corresponding correlation coefficients for the 715 patients of Bigger et al. (1992). LF = low-frequency power (0.04–0.15 Hz); HF = high-frequency power (0.15–0.40 Hz); HR = heart rate; SDNN = standard deviation of normal R–R intervals; r-MSSD = root-mean-square successive difference; pNN50 = percentage of differences between adjacent normal R–R intervals >50 ms. ***P < 0.0001 (Spearman rank order correlation coefficient).

Although cardiovascular autonomic neuropathy is a common and potentially life-threatening complication in Guillain–Barré syndrome (Truax, 1984; Singh et al., 1987; Hughes, 1990; de Jager and Sluiter, 1991; Ropper et al., 1991), quantitative tests have rarely been used to assess such patients. This has been attributed to the fact that severely affected patients are unable to perform standardized tests of autonomic function in an appropriate fashion (Flachenecker et al., 1997). PSA of heart rate variability is non-invasive and easily applicable, requiring no active motor tasks, and is therefore feasible, even in comatose patients (van Ravenswaaij Arts et al., 1993).

Persson and Solders (1983) described a reduction of the standard deviation of R–R intervals in six patients with Guillain–Barré syndrome with subsequent recovery closely paralleling the improving clinical course. Two further studies corroborated these observations showing a transient impairment of autonomic function as estimated by measures in the time domain (Frison et al., 1980; Heinonen et al., 1982). Recently, we have described the temporal course of autonomic dysfunction by using standardized autonomic tests in 13 patients with Guillain–Barré syndrome and demonstrated a significant reduction of parasympathetic and sympathetic function at the height of the disease, with a gradual recovery up to 1 year, closely following the clinical course of the disease (Flachenecker et al., 1997). However, 23% of our patients could not be evaluated during the early stages, and 24–51% of single tests were missed due to motor deficits, facial paresis or mechanical ventilation. Using spectral analysis, autonomic dysfunction could be reliably assessed in all our patients, even in those requiring mechanical ventilation. Thus, we were now able to extend our previous findings to patients being mechanically ventilated (demonstrating a significant reduction of HF power as a measure of parasympathetic tone during the acute stages of Guillain–Barré syndrome). After 1 year, the HF component was significantly increased, with a gradual improvement developing over time. However, LF power was essentially unaltered during the different disease stages; this might be due

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<th>LF</th>
<th>HF</th>
<th>LF : HF</th>
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<tr>
<td>HR</td>
<td>72</td>
<td>-0.52***</td>
<td>-0.55***</td>
</tr>
<tr>
<td>SDNN</td>
<td>72</td>
<td>0.87*** (0.89)</td>
<td>0.83*** (0.82)</td>
</tr>
<tr>
<td>r-MSSD</td>
<td>72</td>
<td>0.78*** (0.65)</td>
<td>0.89*** (0.92)</td>
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<tr>
<td>pNN50</td>
<td>72</td>
<td>0.61*** (0.64)</td>
<td>0.79*** (0.89)</td>
</tr>
<tr>
<td>LF</td>
<td>72</td>
<td>0.78*** (0.77)</td>
<td>0.44*** (0.49)</td>
</tr>
<tr>
<td>HF</td>
<td>72</td>
<td>-0.15 (0.18)</td>
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Correlation coefficients of LF, HF and the LF : HF ratio versus parameters estimated in the time domain in 13 Guillain–Barré syndrome patients, each studied during six disease stages. n = number of pairs available (values <78 indicate missing spectral parameters due to frequent premature beats). The numbers in brackets denote the corresponding correlation coefficients for the 715 patients of Bigger et al. (1992). LF = low-frequency power (0.04–0.15 Hz); HF = high-frequency power (0.15–0.40 Hz); HR = heart rate; SDNN = standard deviation of normal R–R intervals; r-MSSD = root-mean-square successive difference; pNN50 = percentage of differences between adjacent normal R–R intervals >50 ms. ***P < 0.0001 (Spearman rank order correlation coefficient).
to the varying proportions of sympathetic and parasympathetic influences contributing to this frequency band during recovery. As reflected by the diminution of HF power, the sympato-vagal balance at the height of the disease was shifted to sympathetic predominance. This does not contradict our previous finding showing an involvement of both sympathetic and parasympathetic systems, since the LF : HF ratio conveys information about the sympato-vagal balance rather than reflecting absolute sympathetic activity. Our data provide further evidence that autonomic dysfunction in Guillain–Barré syndrome may be caused predominantly by an involvement of the vagal nerves, which might be due to the long myelinated course within the preganglionic parasympathetic nervous system rendering them particularly susceptible to the inflammatory attack of this demyelinating disorder (Zochodne, 1994; Flachenecker et al., 1997).

Since spectral parameters can be influenced by various drugs (van Ravenswaaij Arts et al., 1993; Pieper and Hammill, 1995), we cannot rule out the possibility that the medication administered to our patients may account, at least in part, for the changes observed in the power spectrum. This may apply in particular to patients requiring mechanical ventilation who received the highest amount of autonomically active medication. Mechanical ventilation itself may also have profound effects on afferent inputs and on central respiratory rhythm generation. However, by analysing the individual time courses of spectral parameters, there were no substantial differences between the different groups of patients: those in need of mechanical ventilation; those with additional medication; and those without such treatment, although HF and LF power in mechanically ventilated patients seemed to be lower during the height of the disease. This may also be attributed to the more severe disability present in these patients, since we (Flachenecker et al., 1997) and others (Truax, 1984; Ropper, 1994; Sedano et al., 1994) have shown that autonomic dysfunction was more pronounced in severely affected patients, and particularly so in patients requiring mechanical ventilation (Winer and Hughes, 1988; Hund et al., 1993). Moreover, the time courses of the spectral parameters were essentially similar in the subgroup of patients who did not receive medication compared with those obtained in the whole study group, as well as in those who were not mechanically ventilated. Thus, the influence of medication and mechanical ventilation was probably only minor, as we have previously proposed (Flachenecker et al., 1997).

Clinically overt autonomic dysfunction is present in approximately two-thirds of patients with Guillain–Barré syndrome (Truax, 1984; Singh et al., 1987; Hughes, 1990; Ropper et al., 1991) and encompasses a wide range of cardiac arrhythmias including serious bradycardias and sinus tachycardia (Arnason and Soliven, 1993; Ropper, 1994; Zochodne, 1994). While sustained sinus tachycardia is the most common abnormality, usually not requiring treatment (Ropper, 1994; Arnason and Soliven, 1993; Truax, 1984; Ropper et al., 1991), vagally mediated arrhythmias, such as profound bradycardia or cardiac arrest, are more ominous and may necessitate administration of atropine or insertion of a cardiac pacemaker (Arnason and Soliven, 1993; Flachenecker et al., 1996).
The mechanisms of sinus tachycardia are still a matter of controversy. In some instances tachycardia responded to carotid sinus stimulation providing evidence that the integrity of vagal conduction was at least in part preserved (Truax, 1984). Therefore, Truax (1984, 1988) suggested that the tachycardia was unlikely to be due to a simple vagal denervation. He postulated a ‘phase-dependent block’ based on slowing due to demyelination on either the afferent or vagal efferent (or both) limbs of the baroreflex loop, which would cause impulses to arrive at the sinus node during a relatively refractory period, resulting in tachycardia. In other patients, there was no response to carotid sinus stimulation, with the heart rate being unaffected by respiration or the Valsalva maneuver pointing to a direct vagal damage (Lichtenfeld, 1971). Also, a reduced heart rate acceleration was found in response to atropine, implying a parasympathetic defect (Bansal et al., 1987; Ropper, 1994). Furthermore, abnormal baroreflex sensitivity was noted in four out of seven patients tested (Tuck and McLeod, 1981).

In our study, the power of both frequency bands was strikingly diminished in patients with tachycardia. Interestingly, the LF : HF ratio was similar in patients with and without tachycardia. This might simply be explained by the fact that vagal withdrawal predominantly stimulates the resting heart resulting in tachycardia. Alternatively, cardiac sympathetic fibres might also be involved, abolishing the expected rise in the LF : HF ratio. This hypothesis is further supported by the findings of our previous study demonstrating that tachycardia was significantly related to reduced sympathetic vasomotor function (Flachenecker et al., 1997). Therefore, the tachycardia recorded in our patients could be caused by lesions of the afferent arc of the baroreflex loop, or by damage of efferent vagal fibres.

Abnormal sensitivity to eyeball pressure testing may indicate serious bradyarrhythmias in patients with Guillain–Barré syndrome (Flachenecker et al., 1996). This test reveals parasympathetic overactivity, since the decrease in heart rate could be completely prevented by the administration of atropine (Englert et al., 1985). The results of the present study are in accordance with these observations. As expected, the LF : HF ratio remained essentially unchanged in patients with abnormal responses to eyeball pressure. However, LF power and particularly HF power were significantly increased in patients showing vagal over-reactivity. Further studies are needed to show whether spectral analysis of heart rate variability can identify life-threatening complications in patients with Guillain–Barré syndrome.

References


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