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Detection of serious bradyarrhythmias in Guillain-Barré syndrome: sensitivity and specificity of the 24-hour heart rate power spectrum

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This study was undertaken to determine the nature of bradyarrhythmic events and their relationship to motor disability, disease stages and tachycardia in patients with Guillain-Barré syndrome, and to investigate the potential of the 24-hour heart rate power spectrum (HRPS) for the detection of serious bradyarrhythmias in individual patients. Thirty-five consecutive patients with Guillain-Barré syndrome who were admitted to the authors' intensive care unit were studied. In all patients, the heart rate was continuously recorded during the early stages of the disease, averaged at 1-minute intervals, and stored for 1 to 87 days. The HRPS (n = 556, 16 ± 19 per patient; median, 9) was calculated by Fourier analysis of 24-hour recordings and logarithmically transformed. The slope was estimated by regression analysis of log (power) on log (frequency) between 10^{-4} and 4×10^{-3} Hz, showing an inverse power law behavior in all 556 HRPSs. Eleven patients (31%) had serious bradyarrhythmias. Most of these patients were not dependent on mechanical ventilation, with 3 of 11 patients (27%) still being able to walk more than 5 meters. Sustained tachycardia occurred less frequently in patients with than in those without bradyarrhythmias. The combination of the slope of the power law regression line and the log (power) at 10^{-4} Hz (log P4) of the 24-hour HRPS correctly identified 8 of 11 bradyarrhythmic patients (sensitivity 73%) and 16 of 22 patients with Guillain-Barré syndrome who did not have bradyarrhythmias (specificity 73%). All bradyarrhythmic patients could be detected in the subgroup of patients without sustained tachycardia. The 24-hour HRPS is a powerful predictor of serious autonomic complications in patients with Guillain-Barré syndrome and may help to identify patients at risk of potentially life-threatening arrhythmias.

Key words: Guillain-Barré syndrome, autonomic dysfunction, bradyarrhythmia, heart rate variability, power spectrum analysis.

The Guillain-Barré syndrome (GBS) is an inflammatory, demyelinating disorder of the peripheral nervous system that is assumed to result from aberrant immune responses directed against components of peripheral nerve [1,2]. The clinical features consist of an acutely or, more often, subacutely evolving symmetric paresis of all limbs with areflexia and mild sensory deficits; mechanical ventilation may be required in up to 30% of patients [3,4]. Autonomic neuropathy is a common and important feature and may be present in cardiovascular, sudomotor, gastrointestinal, and other systems, involving both parasympathetic and sympathetic fibers [5]. In particular, vagal overreactivity may cause serious bradyarrhythmias ranging from bradycardia to asystole, which account for a significant number of deaths [5]. It is generally believed that these bradyarrhythmias occur only in severely disabled patients, mainly in patients requiring mechanical ventilation [6–9]. However, they also have been described in cases without mechanical ventilation and even in less severely affected patients [8,10,11]. Early recognition of these potentially life-threatening dysrhythmias is crucial for the initiation of appropriate preventive therapy such as external cardiac pacemakers or monitoring on the intensive care unit (ICU). However, clinical studies disagree on which patients should be regarded at risk.

Eyeball pressure is a strong stimulus for producing asystole [9,12]. We have found that abnormal sensitivity to eyeball pressure testing correctly identified two of three patients needing cardiac pacing or cardiopulmonary resuscitation because of sinus arrest [11]. One drawback of this method is the lack of a reproducible and quantitative stimulation. Adverse effects may include retinal damage or a profound bradycardia leading to asystole, which makes it necessary to keep safeguards for prompt and appropriate resuscitation in place [11]. In a subsequent evaluation, we found that the regression line of spectral power on frequency of the 24-hour heart rate power spectrum (HRPS) discriminated better between patients with and without abnormal sensitivity to eyeball pressure testing than the heart rate variability parameters derived from 5 minutes at rest or from standard autonomic function tests [13]. However, the potential to detect serious bradyarrhythmias has not been studied. Furthermore, cutoff values for this measure were not available, which makes identifying individual patients at risk difficult, and the sensitivity and specificity remain to be determined.

This study aims at (1) describing retrospectively the nature of bradyarrhythmic events and their relationship to motor disability, disease stages, and tachycardia in a large

cohort of 35 patients with GBS who were admitted to the ICU, and (2) investigating the potential of the 24-hour HRPS for the detection of serious bradyarrhythmias in individual patients.

Patients and methods

Patients

Between July 1993 and December 1996, 42 patients with GBS were admitted to the ICU of our department. The diagnosis was based on (1) clinical features, ie, progressive weakness of two or more limbs for less than 4 weeks, and absent or reduced tendon reflexes, (2) cerebrospinal fluid leukocyte count less than 50/μl, and (3) absence of other causes, eg, porphyria, toxins, systemic vasculitis, diphtheria, or botulism [14]. Three patients were excluded because of missing heart rate data, and in four patients, detailed medical records were not available.

Thus, 35 patients were included in this study (11 women, 24 men; mean age, 52.4 y; age range, 18–81 y; median, 55 y). Thirteen of these patients were part of a prospective, longitudinal study of autonomic function in GBS [11,13]. The mean disability score (DS; see later discussion) at admission was 3.5 (range 2 to 5, median 4), whereas the worst disability score was 4.0 (range 2 to 5, median 4). The duration of the progressive phase was 8.5 ± 6.6 days (mean ± standard deviation, range 2 to 39, median 7) and of the plateau phase, 6.0 ± 8.1 days (range 0 to 31, median 3). Nine of 35 patients (26%) required mechanical ventilation for 7 to 47 days. No patient died during the study period.

Fourteen patients were treated with plasmapheresis, seven with intravenous immunoglobulins, and 10 with a combination of both. Four patients received no specific therapy. Symptomatic treatment included heparin, antacids, mucolytics, antibiotics, analgesics, narcotics, sedating, and antihypertensive agents and was allowed at the discretion of the treating physician. The most frequent preexisting disease was arterial hypertension in 10 patients; other concomitant conditions included diabetes mellitus (n = 5), cardiac arrhythmias (n = 3), coronary artery disease (n = 2), heart failure (n = 2), chronic obstructive pulmonary disease (n = 2), and chronic alcohol abuse (n = 2).

24-Hour heart rate power spectrum (HRPS)

The heart rate was continuously recorded during the early stages of the disease, ie, as long as the patient was judged to require ICU monitoring (GISI Data Management System; PPG Hellige Ltd., Freiburg i. Br., Germany). Within this system, the heart rate was averaged at 1-minute intervals and stored on hard disk. The extracted 1-minute heart rate data were plotted as a tachogram, and the HRPS was calculated by harmonic Fourier analysis of consecutive, nonoverlapping 24-hour recordings encompassing data sets of 1,440 values as described previously [13]. In total, 556 HRPSs were available in 35 patients (16 ± 19 per patient, mean ± standard deviation, range 1–87, median 9). Single missing heart rate data and artifacts (which were automatically detected by a >50% change in the succeeding heart rate with visual check) were replaced by linear interpolation, and the resulting power first underwent frequency averaging at every fourth value. After log transformation of power and frequency, the spectrum was smoothed by integrating power into bins spaced 60 per decade, ie, 0.0167 log (Hz) wide [13,15]. The slope of the regression line of each of the 556 HRPSs was estimated by simple linear regression analysis of log (power) on log (frequency) in the scaling region between 10^{-4} and 4×10^{-3} (0.004) Hz, thus avoiding interferences with periodic components at 0.01 Hz [15,16]. This measure has been shown to provide insights into the sympathovagal balance [15] and was flatter, ie, less negative, in patients with vagal overreactivity, and steeper, ie, more negative, in patients with tachycardia [13]. In addition, the log (power) at 10^{-4} Hz was taken from the HRPS, constituting the "log P4" which quantifies oscillations ranging approximately 3 hours (Fig. 1).

Disability score, disease stages, and clinical autonomic dysfunction

The clinical characteristics of the patients were taken from the medical records, which include the findings of a complete neurologic examination at least once per day, a detailed description of heart rate and blood pressure changes, and careful notification of any unusual events during the time on the ICU. The charts were reviewed independently by two investigators (Dr. Peter Flachenecker and Kristine Lem).

The DS was graded on an ordinal scale from 0 to 5 as follows: (0) healthy, no signs or symptoms attributable to GBS; (1) minor symptoms or signs and capable of running; (2) able to walk 5 meters across an open space without assistance, walking frame, or stick, but unable to run; (3) able to walk 5 meters across an open space with the help of one person and waist-level walking frame, stick, or sticks; (4) chair bound/bed bound; unable to walk as in 3; and (5) requiring assisted ventilation (for at least part of day or night) [17].

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 to 28 days after start of recovery), and late remission (more than 28 days after the first signs of improvement).

Sustained tachycardia was defined as heart rate above 100 beats/min, which required confirmation by a second measurement at least 1 hour later. Serious bradyarrhythmias were considered (1) sustained asystole requiring cardiac pacing or cardiopulmonary resuscitation, (2) bradycardia, defined as heart rate below 40 beats/min, necessitating the administration of atropine, (3) bradycardia below 40 beats/min with spontaneous recovery, and (4) abnormal sensitivity to eyeball pressure testing (EP), defined as a decrease of the heart rate below 40 beats/min during the maneuver, which was performed as part of a longitudinal study [11]

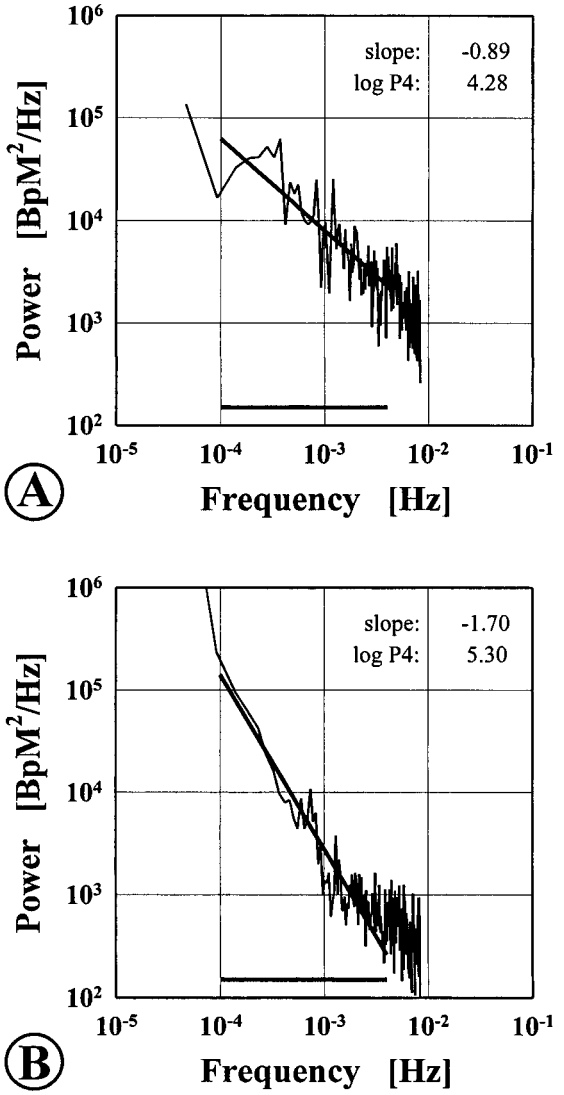

Figure 1. Twenty-four-hour heart rate power spectra (HRPS) in two patients with Guillain-Barré syndrome (GBS). Individual plots of log (power) versus log (frequency) constituting the 24-hour heart rate power spectrum (HRPS) in (**A**) a patient who repeatedly required cardiac pacing (patient 11, Table 1) and (**B**) a similarly disabled patient who never experienced serious bradyarrhythmias. The horizontal bars at the bottom of each graph indicate the scaling region between 10^{-4} and 4×10^{-3} Hz. The slope was flatter, ie, less negative, and the log P4 was lower in the bradyarrhythmic patient (**A**) compared with the control patient (**B**).

and, thereafter, routinely at the discretion of the attending physician to assess the risk for impending bradyarrhythmia.

Statistics

Nonparametric tests were used for all comparisons. Differences between patient groups were analyzed by the Mann-Whitney rank sum test, and correlation coefficients were calculated by Spearman rank order correlation. A proportion of patients were compared with Fisher exact test and the chi-square test, respectively (standard software package, SIGMAStat for Windows Version 1.0; Jandel Corporation, San Rafael, CA). Results were considered statistically significant for $p < 0.05$.

Results

Clinical autonomic dysfunction

Bradyarrhythmic events (asystole requiring cardiopulmonary resuscitation, cardiac pacing or atropine, and abnormal sensitivity to EP) occurred at least once in 11 of 35 patients (31%) during the early course of GBS. In eight of these patients, bradyarrhythmias were repeatedly noted, yielding a total of 33 events (Table 1). Most of these complications fell into the progressive and plateau phase of the disease; only two patients experienced one of these events for the first time during the early remission phase. None suffered from bradyarrhythmias more than 20 days after the onset of clinical recovery. Age (52.2 ± 15.9 vs 52.5 ± 12.0, mean ± standard deviation), gender (female/male ratio 3/8 vs 8/16) and disability scores (3.9 ± 1.1 vs 4.0 ± 0.8) were similar in patients with and without bradyarrhythmias. Although arrhythmic complications mainly occurred in severely disabled patients (DS 4–5), a considerable proportion (3 of 11, 27%) experienced bradycardia while still being able to walk more than 5 meters with help (DS 3) or even without any help (DS 2, Table 1). The proportion of patients requiring mechanical ventilation was slightly higher in the bradyarrhythmic group (4 of 11, 36%) compared with the patients without this complication (5 of 24, 21%), but this difference failed to reach statistical significance ($p = 0.42$). Tachycardia was present in 22 of 35 patients (63%) and occurred less frequently in patients with than in those without bradyarrhythmias (4 of 11, 36% vs 18 of 24, 75%, $p = 0.0571$, Fisher exact test).

Influence of concomitant conditions and medication

The preexisting diseases and concomitant medication of the 11 bradyarrhythmic patients are listed in Table 2. Mechanically ventilated patients received the highest amount of medication, mainly sedatives. β-Blocking agents were administered to three patients. However, only one of four bradyarrhythmic episodes of one patient (patient 1) occurred while taking β-blockers. Another patient (patient 4) was treated with β-blockers because of cardiac arrhythmia before the onset of GBS, with unchanged medication during the course of the disease. Preexisting bradyarrhythmia was noted in one patient (patient 7) who was not treated before GBS but required atropine repeatedly during the early course of the disease.

24-Hour heart rate power spectrum (HRPS)

Twenty-six HRPSs of 11 patients with bradyarrhythmias were available for analysis and were compared with 42 HRPSs obtained from 22 patients matched for age, worst disability score, and disease stages ("matched controls"). More than one HRPS was available in five bradyarrhythmic and eight control patients because of repeatedly occurring bradyarrhythmias (Table 1). In these patients, the mean slopes and log P4 of all individual HRPS were used for further analysis.

Figure 2 shows the group values for the slope and log P4 of the bradyarrhythmic patients (BA), of these patients

Table 1. Clinical characteristics of 11 patients with Guillain-Barré syndrome and bradyarrhythmic events

Patient	Age	Gender	DS	Phase	Tachycardia	No. of events*	Events
1	21	F	5	PRP–PLP	Yes	4 (4)	EP
2	56	F	5	PRP	Yes	2 (1)	CPR, EP
3	55	M	5	PLP	No†	2 (2)	Pacing
4	68	M	3	RMP_e	No	1 (1)	BA
5	56	M	4	PRP	No	2 (1)	BA, EP
6	65	F	4	PLP	No	1 (1)	BA
7	64	M	2	PRP–RMP_m	No	5 (5)	Atropine, BA
8	44	M	5	PRP–RMP_m	Yes	6 (5)	Atropine, EP
9	70	M	4	RMP_e	No	1 (1)	BA
10	56	M	2	PLP–RMP_m	No	4 (1)	EP
11	29	M	4	PRP	No	5 (4)	Pacing, EP

DS, worst disability score during the disease [17] (see Methods for detailed description); PRP = progressive phase; PLP = plateau phase; RMP_e = early remission phase (<7 days); RMP_m = middle remission phase (7–28 days); EP = abnormal response to eyeball-pressure testing. CPR = cardiopulmonary resuscitation; Pacing = cardiac pacing; Atropine = bradyarrhythmia necessitating atropine; BA = bradyarrhythmia <40 beats per minute, with spontaneous recovery.
*Numbers in parentheses denote the numbers of events for which 24-hour heart rate data were available.
†This patient demonstrated tachycardia during 3–4 days, 8–11 days before bradyarrhythmias developed.

during the remission phase (ie, of the last day on the ICU), without further bradyarrhythmias (BA'), and of the 22 control patients (CO). The median slope was higher, ie, less negative, in the BA patients compared with the controls, although this difference fell short of statistical significance ($p = 0.11$). During clinical recovery (BA'), the slopes approached that of the CO group (Fig. 2A). Log P4 was significantly lower in the BA patients compared with the controls, with an increase during clinical remission (Fig. 2B).

Visual inspection of the scatter plots of log P4 versus slope indicates that BA and CO patients were best discriminated by cutoff values of -1.2 and 4.9 for the slope and log P4, respectively (Fig. 3). Six of 11 bradyarrhythmic patients

Table 2. Pre-existing diseases and concomitant medication of 11 patients with bradyarrhythmia

Patient	Pre-existing diseases	Concomitant medication
1	—	Sedatives, β-blocker,* calcium antagonist*
2	Hypertension	Sedatives
3	—	Sedatives, β-blocker, carbamazepine
4	Cardiac arrhythmia, coronary artery disease	β-blocker†
5	Hypertension, heart failure	Diuretics,† ACE inhibitor†
6	Hypertension	—
7	Hypertension, bradyarrhythmia‡	Diuretics†
8	—	Sedatives
9	Diabetes mellitus	—
10	—	—
11	—	—

All patients received heparin, antacids, and mucolytics.
ACE = angiotensin-converting enzyme.
*Only in one of four bradyarrhythmic occurrences.
†Pre-existing medication, unchanged during the disease course.
‡No treatment required previously.

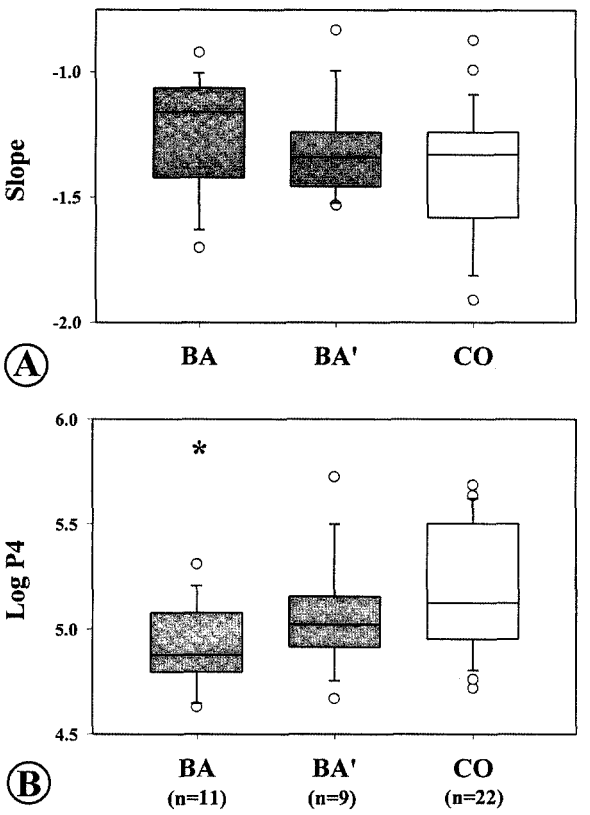

Figure 2. Parameters of the 24-hour heart rate power spectrum in bradyarrhythmic patients and controls. The slope of the power law regression line (**A**) and the log (power) at 10^{-4} Hz (**B**) in 11 bradyarrhythmic patients (BA), nine bradyarrhythmic patients during clinical recovery (BA'), and 22 matched control patients (CO). Boxes, 25%–75% quartiles; whiskers, 10%–90% percentiles; solid lines, median values; circles, single values outside the 10% and 90% percentiles. (**A**) The median slope was higher, ie, less negative, in the BA patients compared with the controls, although this difference failed to reach statistical significance ($p = 0.11$). During clinical recovery (BA'), the slopes approached that of the CO group. (**B**) Log P4 was significantly lower in the BA patients compared with the controls, with an increase during clinical remission. *$p < 0.04$, BA versus CO, Mann-Whitney rank sum test.

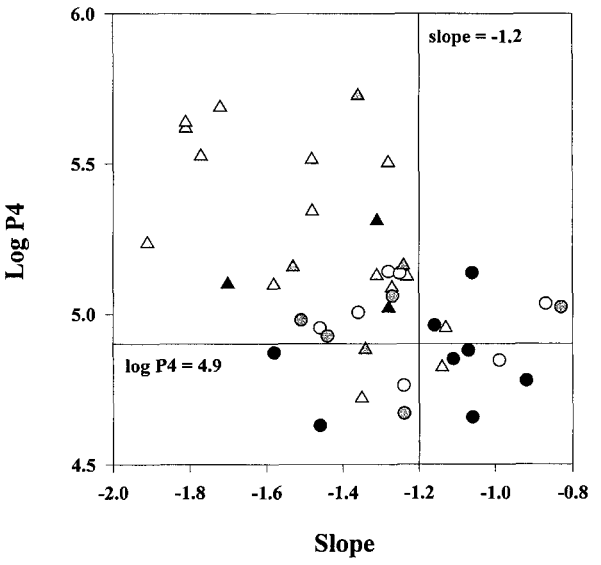

Figure 3. Log P4 versus slope for bradyarrhythmic patients and controls. Scatter plot of log (power) at 10^{-4} Hz (log P4) versus slope for 11 bradyarrhythmic patients (black symbols), nine bradyarrhythmic patients during clinical recovery (gray symbols), and 22 matched control patients (white symbols). The triangles denote patients with sustained tachycardia. The cutoff values (slope = –1.2, log P4 = 4.9) are shown on the graph. Eight of 11 patients with bradyarrhythmias demonstrated a slope ≥–1.2 or a log P4 <4.9, yielding a sensitivity of 73%, whereas 16 of 22 control patients fell outside these ranges (specificity 73%, p <0.025; Fisher exact test).

showed a slope ≥–1.2, resulting in a sensitivity of 55%, whereas only 4 of 22 control patients fell into this range (specificity 82%). Similar results were found for log P4 <4.9 (6/11 BA vs 4/22 CO patients; sensitivity 55%, specificity 82%). However, considering patients with a slope ≥–1.2 *or* log P4 <4.9 at risk for bradyarrhythmias resulted in a considerable increase in sensitivity (73%), with only a slight decrease in specificity (73%; Fig. 3 and Table 3). Moreover, all BA patients without tachycardia (T–, Table 3) could be correctly identified with this combined measure. These numbers were similar when bradyarrhythmic events rather than patients were analyzed, or when all available HRPS (in total 556) of all 35 patients were taken into account (Table 3).

Table 4. Correlation of heart rate power spectrum to length of observation period

	2 Days	3 Days	4 Days	7 Days
24 Hours	0.90 (49)	0.85 (45)	0.83 (37)	0.71 (32)
2 Days		0.97 (43)	0.96 (37)	0.89 (32)
3 Days			0.98 (37)	0.94 (32)
4 Days				0.96 (32)

Correlation coefficients between the slopes of the regression line obtained from the 24-hour heart rate power spectrum, and the mean of the slopes derived from 2-, 3-, 4-, and 7-day recordings of 11 patients with bradyarrhythmic events (N = 26) and 22 matched controls (N = 42).
The numbers in brackets denote the pairs available.
All comparisons are statistically significant (p <0.001).

Effect of data recording period

To study the robustness of our data and to determine the optimal observation period, we calculated the mean HRPS of 2, 3, 4, and 7 days and correlated the findings to the 24-hour HRPS of 1 day in the 26 BA and 42 CO recordings. Overall, there was a highly significant correlation between the various observation periods (Table 4). This indicates the reliability of our data and provides evidence that the calculation of a 1-day HRPS was sufficient for the detection of bradyarrhythmias.

Discussion

The main findings of our study were that serious bradyarrhythmias occurred in one third of our patients with GBS, of whom 27% were still able to walk more than 5 meters. Bradyarrhythmic events could not be predicted by the degree of disability, the necessity for mechanical ventilation, or the presence of tachycardia. However, the combined measure slope or log P4 of the 24-hour HRPS reliably identified individual patients at risk of serious bradyarrhythmias and was particularly useful in patients without tachycardia.

Dysautonomia in GBS

On routine clinical examination, autonomic dysfunction is present in approximately two thirds of patients with GBS

Table 3. Sensitivity and specificity of the 24-hour heart rate power spectrum

	Matched pairs				All measures	
	Patients		Events		Events	
	All*	T–*	All†	T–‡	All§	T–§
Sensitivity	73% (8/11)	100% (8/8)	77% (20/26)	94% (16/17)	77% (20/26)	94% (16/17)
Specificity	73% (16/22)	57% (4/7)	74% (31/42)	50% (8/16)	60% (316/530)	51% (104/202)

Sensitivity and specificity for the detection of bradyarrhythmias of the combined outcome measure slope ≥–1.2 and/or log P4 <4.9 of the 24-hour heart rate power spectrum.
All = all patients or events; T– = subgroup of patients or events without tachycardia.
*p <0.025 (Fisher exact test).
†p <0.0001 (Fisher exact test).
‡p <0.01 (Fisher exact test).
§p <0.001 (χ^2 test).

[2,18–20], and even in 90% when standard autonomic function tests are applied [21]. In line with the results of the current study, sinus tachycardia is the most common though usually harmless abnormality [22,23]. Vagally mediated arrhythmias such as bradycardia and heart arrest are more ominous and may require atropine or cardiac pacemakers, as could be seen in our patients. The incidence of bradycardia differed between clinical studies and ranged from 7% to 34% [6,7,22–24]. The relatively high frequency of 31% in our patients compared with others [7,22] might be attributable to our definitions, which included abnormal sensitivity to eyeball pressure as a bradyarrhythmic event. However, this approach seems reasonable because the results of eyeball pressure testing were correlated to arrhythmic episodes requiring cardiac pacing or cardiopulmonary resuscitation [11], thus indicating that this stimulus may be used reliably as an indicator for serious bradyarrhythmias. Although we cannot completely rule out that preexisting diseases and concomitant medication may account at least in part for some of the bradyarrhythmias, we believe this possibility unlikely for the following reasons: First, the only patient with preexisting bradyarrhythmia did not require treatment with parasympatholytics before falling ill with GBS, whereas he did so during the early course of the disease. Second, β-blocking agents and calcium channel antagonists were taken during two bradyarrhythmic episodes, whereas two further events occurred in the same patient when not taking these drugs. Finally, β-blocking therapy for cardiac arrhythmias was unchanged before, during, and after GBS, with a bradyarrhythmic event occurring only during the plateau phase. Thus, preexisting cardiac arrhythmias and autonomically active medication may predispose patients to develop serious bradyarrhythmias, but cannot solely account for these complications.

None of our patients died, which is in line with the results of recent studies showing that there were no deaths clearly linked to autonomic dysfunction [25,26]. This may reflect the heightened awareness of this potentially life-threatening complication and the early use of cardiac monitoring, as in our patients. However, 4 of the 10 deaths in the series of Winer *et al.* [27], and 7 of the 33 deaths in the Italian multicenter study [28] were related to cardiac arrest; five of the latter deaths occurred despite monitoring on the ICU [28]. This underscores the importance of dysautonomia as a major cause of death in the modern era and, therefore, identifying patients with GBS who are at risk is of utmost clinical importance for the initiation of preventive therapies.

Serious bradyarrhythmias and clinical characteristics

Serious bradyarrhythmias have been thought to occur only in severely disabled patients, mainly in those who needed artificial ventilation [8]. In the series of Winer and Hughes, only those patients requiring mechanical ventilation developed serious arrhythmias [7]. The incidence of bradycardia was 44% in quadriplegic or ventilated patients, compared with 2% to 7% in those who were less severely disabled [6]. However, we [11] and others [8,10] have described patients who suffered from serious bradyarrhythmias before needing ventilation and during weaning from the ventilator. Some patients were only moderately affected by the disease. These observations are corroborated by the results of the current study, which show virtually no difference in the disability scores between patients with bradyarrhythmias and those without. Although the proportion of patients requiring mechanical ventilation was slightly higher in the bradyarrhythmic group, this difference fell far from statistical significance. Moreover, most of our patients experienced bradyarrhythmias while not ventilated, and one third suffered from this complication while still being able to walk more than 5 meters. The high incidence of arrhythmias in less severely disabled patients might be attributable to our close monitoring on the ICU, which more truly reflects the incidence of serious bradyarrhythmias in patients with GBS.

Another factor thought to predict serious bradyarrhythmias is sustained sinus tachycardia, which was significantly more frequent in patients with than in those without arrhythmias [7]. In our study, the opposite was true: tachycardia occurred in only 36% of bradyarrhythmic patients, compared with 75% of those without cardiac arrhythmia. This is not surprising because sinus tachycardia usually results from loss of vagal efferent innervation, whereas serious bradyarrhythmias are caused by vagal overreactivity rather than impairment [5]. Thus, risk prediction of serious autonomic complications based solely on severe disability (ie, patients requiring mechanical ventilation) or sustained tachycardia may be misleading and potentially dangerous in the management of patients with GBS.

24-Hour heart rate power spectrum

The long-term heart rate variability over 10 to 24 hours has been examined in healthy volunteers, showing that the plot of power and frequency on a log-log graph could be described by a straight line with a slope close to −1; this indicates that the power decreased in proportion to the reciprocal of frequency [29,30]. Denervation of the heart results in tachycardia and causes a much steeper slope with a mean of approximately −2. This has been shown in cardiac transplant patients [15]. More interestingly, combining the slope of the power law regression line and the log (power) at 10^{-4} Hz (the so-called log P4) was found to predict death after myocardial infarction better than the traditional spectral bands obtained from 5-minute epochs, independent of routine clinical and laboratory variables [15]. This holds true even for a random population of elderly subjects [31]. In a pilot study of 13 patients with GBS [13], we found that the slope of the regression line could identify both signs of autonomic neuropathy, tachycardia and vagal overreactivity (as indicated by abnormal sensitivity to eyeball pressure testing). Moreover, the slope of the power law regression line proved the best discriminator for vagal overreactivity [13]. The results of the current study confirm and extend these findings: the slope was higher, ie, less negative, and the log P4 was lower in patients with bradyarrhythmias than in those matched for age, disability score, and disease stage, with a subsequent recovery during clinical remission

approaching the values of the control patients. Both parameters could be obtained easily from the 24-hour HRPS by doing simple regression analysis (slope) and extracting the log P4 directly from the log-log plot. To our knowledge, this is the first study providing cutoff values that allow for the identification of individual patients at risk. The combination of both parameters resulted in a sensitivity and specificity of 73%, which were similar when events rather than patients were considered. Specificity dropped slightly to 60% when all available measurements were analyzed. A possible explanation might be that patients of the bradyarrhythmic group who did not show serious bradyarrhythmias at the time of measurement showed a positive test result in the HRPS, indicating subclinical vagal overactivity. This suggests that the analysis of all measurements might even underestimate the specificity of the 24-hour HRPS.

The slopes of patients with tachycardia were lower, ie, more negative, than in those without elevated heart rates [13], and were shifted toward -2, resembling those of denervated hearts [15]. Patients with tachycardia and bradyarrhythmia should thus have intermediate values, resulting in less discriminative power of the 24-hour HRPS. This consideration was corroborated by analyzing only those patients who did not suffer from sustained tachycardia. It is particularly remarkable that all bradyarrhythmic patients and all but one of the bradyarrhythmic events could correctly be identified within this subgroup. Transferring our results into clinical practice, a slope <-1.2 and a log P4 ≥ 4.9 in a given patient without tachycardia indicates that this patient would not develop serious bradyarrhythmias. Thus, the 24-hour HRPS is a powerful predictor of serious autonomic complications in patients with GBS, especially in those without concomitant tachycardia. It may help to identify patients at risk for potentially life-threatening arrhythmias. Implementation of this measure in routine data management systems would provide a continuous and noninvasive parameter for the decision regarding which patient could be safely discharged from the ICU and which patient should continue to be monitored more closely.

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