Noninvasive Exploration of Cardiac Autonomic Neuropathy

Four reliable methods for diabetes?

MICHEL DUCHER, PHD
CATHERINE CERUTTI, PHD
MARIE PAULE GUSTIN, PHD
SAWSAN ABOU-AMARA, MD
CHARLES THIVOLET, MD, PHD
MAURICE LAVILLE, MD
CHRISTIAN ZACHARIE PAULTRE, PHD
JEAN PIERRE FAUVEL, MD, PHD

OBJECTIVE — The purpose of this work was to assess relevant information that could be provided by various mathematical analyses of spontaneous blood pressure (BP) and heart rate (HR) variabilities in diabetic cardiovascular neuropathy.

RESEARCH DESIGN AND METHODS — There were 10 healthy volunteers and 11 diabetic subjects included in the study. Diabetic patients were selected for nonsymptomatic orthostatic hypotension in an assessment of their cardiovascular autonomic impairment. Cardiac autonomic function was scored according to Ewing's methodology adapted to the use of a Finapres device. The spontaneous beat-to-beat BP and HR variabilities were then analyzed on a 1-h recording in supine subjects. The global variabilities were assessed by standard deviation, fractal dimension, and spectral power. The cardiac baroreflex function was estimated by cross-spectral sequences and *Z* analyses.

RESULTS — In diabetic patients, Ewing's scores ranged from 1 to 4.5, confirming cardiovascular autonomic dysfunction. In these diabetic patients, global indices of variabilities were consistently lower than in healthy subjects. Furthermore, some of them (standard deviation and fractal dimension of HR, spectral power of systolic blood pressure and HR) were significantly correlated with the Ewing's scores. The *Z* methods and the spectral analysis found that the cardiac baroreflex was less effective in diabetic subjects. However, the baroreflex sensitivity could not be reliably assessed in all the patients. The sequence method pointed out a decreased number of baroreflex sequences in diabetic subjects that was correlated to the Ewing's score.

CONCLUSIONS — Indices of HR spontaneous beat-to-beat variability are consistently related to the degree of cardiac autonomic dysfunction, according to Ewing's methodology. The *Z* method and spectral analysis confirmed that the cardiac baroreflex was impaired in diabetic patients. These methods might be clinically relevant for use in detecting incipient neuropathy in diabetic patients.

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From the Département de Néphrologie et Hypertension Artérielle (M.D., M.L., J.P.F.) and the Département d'Endocrinologie, Diabète, Nutrition (S.A.-A., C.T.), Hopital E. Herriot; and the Département de Physiologie et Pharmacologie Clinique (M.D., C.C., M.P.G., C.Z.P.), Faculté de Pharmacie, Lyon, France.

Address correspondence and reprint requests to J.P. Fauvel, Département de Néphrologie et Hypertension Artérielle, Hopital E. Herriot, 69437 Lyon, France.

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Abbreviations: BP, blood pressure; BRS, baroreflex sensitivity; dBP, diastolic blood pressure; HF, high frequency; HR, heart rate; LF, low frequency; RD, relative dispersion; sBP, systolic blood pressure; VLF, very low frequency.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Noninvasive exploration of the autonomic nervous system is important for scientists and physicians because cardiac autonomic nervous system dysfunction is a precocious complication in diabetes in which diabetic neuropathy predicts an increased risk in cardiovascular morbidity and mortality (1,2). In autonomic neuropathy, blood pressure (BP) regulation is impaired by both vascular sympathetic and cardiac baroreflex alterations. The current diagnosis of cardiovascular neuropathy is based on a battery of well-established tests stimulating the cardiovascular autonomic system (3). These tests, first described by Wheeler and Watkins (4) and later by Ewing et al. (5), must be rigorously standardized and imply a close cooperation of the subjects.

More simple and reliable methods of detecting and quantifying cardiac dysautonomy are of clinical interest. Autonomic control of BP may be reflected by spontaneous beat-to-beat BP and heart rate (HR) variabilities obtained by a Finapres recording. Various mathematical analysis customized to BP and HR beat-to-beat variations quantify the strength of their relations. Thus, the spectral analysis was reported to provide useful information on autonomic nervous function (6–8). Cardiac baroreflex sensitivity (BRS) was reported to be reliably estimated by cross-spectral analysis (including Fourier analysis, as well as autoregressive modeling), by the sequence method (analysis of linear covariations of systolic blood pressure [sBP] and HR), and by the *Z* method (analysis of the statistical dependence of BP and HR) (9–13). Furthermore, the nonlinear dynamic of the cardiovascular system can be analyzed by the fractal and chaos analysis that quantify its degree of complexity (14–16). All these methods were applied to diabetic subjects to quantify their cardiac dysautonomy, but their relative interest has never been assessed. The purpose of this work, then, was to compare indices of autonomic nervous system function obtained from diabetic subjects exhibiting nonsymptomatic orthostatic hypotension.

RESEARCH DESIGN AND METHODS

Subjects

Ten healthy volunteers (aged 46 ± 4 years) whose biological parameters (serum glucose, complete blood and platelet counts, liver enzymes, serum creatinine, and dipstick urinalysis) were within normal limits and who had a BP <140/90 mmHg were included. There were 11 normotensive diabetic subjects (9 type 1 and 2 type 2 diabetic patients aged 48 ± 5 years) who were selected for nonsymptomatic orthostatic hypotension (systolic BP variation −39 ± 7 mmHg). Any medication known to interfere with BP control was not allowed during the week that separated the selection visit from the experiment day. The protocol was approved by the local Ethics Committee, and written informed consent was obtained from each subject.

BP and HR measurements

BP was recorded using a Finapres device (model 2300, Ohmeda, Englewood, CO) with the cuffed finger held in the mid-axillary position at heart level throughout the procedure. After 10 min of familiarization, the automatic calibration was switched off, and BP was recorded for 1 h. The accuracy of a 1-h BP Finapres recording at rest has been assessed in comparison to an intra-arterial recording (17). Respiration rate was controlled at 0.3 Hz using a metronome. Before each autonomic test, the Finapres was calibrated to obtain a satisfactory BP. Signal acquisition and data processing have been previously described (18).

Ewing's scores

The four conventional autonomic function tests (standing, Valsalva maneuver, deep breathing, handgrip) were performed as described by Ewing et al. (5) and adapted to the use of the Finapres device. Normal values were not adjusted for age as recommended by Low et al. (19) because authors did not give normative values for the 15:30 ratio and the diastolic blood pressure (dBP) increase during the handgrip test. Therefore, we used normative values provided by Ewing in his original paper (5). Scores were assigned as follows: 0 for a normal test, 0.5 for a borderline, and 1 for an abnormal value (Table 1). The sum of the five scores was defined as the Ewing's score.

Spectral analysis

Spectral analysis was performed according to our previously described technique adapted to humans (20). Spectra were computed using a fast Fourier transform analysis on 50% overlapping stationary segments of 512 points resampled every 0.7 s. Spectral power was computed within each band as follows: a very low frequency (VLF) band (0.02–0.07 Hz), a low frequency (LF) band or Mayer's band (0.07–0.14 Hz), and a high frequency (HF) band (0.25–0.35 Hz), and total spectral power was computed over the entire frequency range (0.02–0.70 Hz). The strength of the linear coupling between sBP and HR in each band was expressed as the mean of the coherence function. The average modulus of the transfer functions were taken as indices of BRS if >0.5 (11).

Table 1—*Ewing's scores in diabetic subjects*

	Standard normal values	Borderline values	Diabetic subjects (n = 11)	Pathological responses (n)
Standing up				
Δ sBP (mmHg)	≤10	11–29	39 ± 7	11
15:30 ratio	≥1.04	1.01–1.03	1.04 ± 0.04	7
Deep breathing				
HR min − max (beats/min)	≥15	11–14	14 ± 4	5
Valsalva maneuver				
HR min/max	≥1.21	1.11–1.20	1.20 ± 0.06	8
Handgrip				
Δ dBP (mmHg)	≥16	11–15	30 ± 4	3
Ewing's score	—	—	2.4 ± 0.4	11

Data are means ± SEM.

Z analysis

The statistical dependence between sBP and HR was quantified with the *Z* coefficient computed as follows:

$$Z(\text{sBP, HR}) = [P(\text{HR} \mid \text{sBP}) - P(\text{HR})]/[1 - P(\text{HR})] \quad (1)$$

where P(HR | sBP) represents the estimated conditional probability to observe the HR value if the sBP value is observed and P(HR) is the estimated probability of observing the HR value.

As previously described (20), the data were pooled in intervals of 3 mmHg for sBP and of 2 beats/min for HR. Only (sBP, HR) couples with occurrence >10 were taken into account. The modal class of the bivariate (sBP, HR) distribution was determined, and (sBP, HR) couples were compared with modal class to reflect the baroreflex activity. The slope of the linear regression between these low sBPs and high HRs (or vice versa) was reported to a reliable index of the BRS if the regression coefficient was >0.5.

Fractal analysis

The fractal dimension was estimated by computing standard deviation of time series at different time scales (21). First standard deviation of sBP (or HR), which were computed on the whole recording (n_0 values), gave SD_0. Then, paired consecutive values were averaged, and standard deviation was calculated on this new series of averaged values. This procedure was repeated on series with geometrically decreasing length, grouping values by 4, 8, 16,…, n, n_0. At step n, the relative dispersion (RD_n) of sBP (or HR) was as follows:

$$RD_n = SD_n/\text{mean}$$

The fractal dimension D was given by the linear regression formula (accepted if $P < 0.05$):

$$\log(RD_n) = \log(RD_0) + (1 - D)\log(n/n_0)$$

Sequence analysis

sBP and HR times series were first low-pass filtered at 0.5 Hz and were resampled at 2 Hz. Slopes of the linear regression between opposite changes in sBP and 1 beat–delayed HR changes during at least three consecutive beats were selected for $P < 0.05$. The mean slope of the selected sequences was reported to provide a reliable index of the BRS (12,22).

Statistical analysis

All averaged data are expressed as means ± SE. Results in healthy and diabetic subjects were compared using the Mann-Whitney test. The relations between the estimated indices of

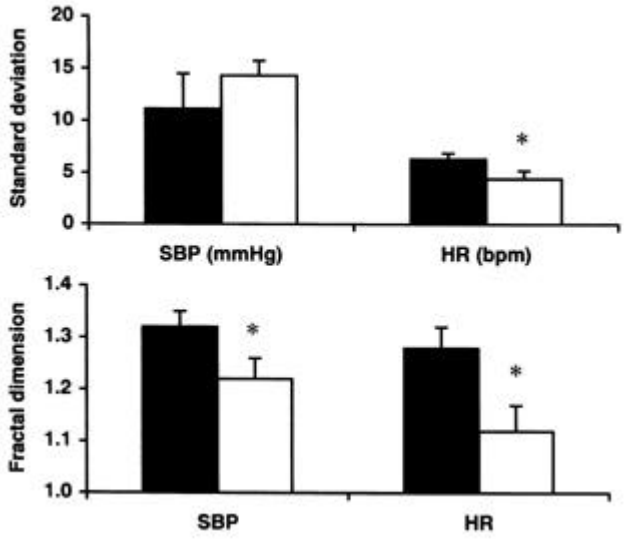

Figure 1—*Standard deviation and fractal dimension of sBP and HR in healthy (n = 10) (■) and diabetic (n = 11) (□) subjects.*

autonomic function obtained by the different methods were evaluated by Spearman's rank correlation coefficient. Results were considered to be significant when $P < 0.05$. The Bonferroni-Dunn test was used to calculate the critical deviation between mean values in each group to obtain a $P = 0.05$.

RESULTS

Ewing's tests

In diabetic patients, Ewing's scores ranged from 1 to 4.5. Average values of indices of autonomic activity are given in Table 1.

Standard deviation

As shown in Fig. 1, the 1-h standard deviation of HR, but not of sBP, was significantly lower in diabetic subjects than in healthy subjects.

Fractal dimension

The fractal dimension of sBP and HR could be assessed during the 1-h recording in all subjects. Figure 1 shows that it was significantly lower in diabetic patients than in healthy volunteers, for both sBP and HR.

Spectral analysis of sBP and HR

The total spectral power of HR was significantly lower in diabetic subjects than in healthy subjects. Both sBP and HR spectral powers in the LF and HF bands were significantly lower in diabetic patients than in healthy subjects (Fig. 2).

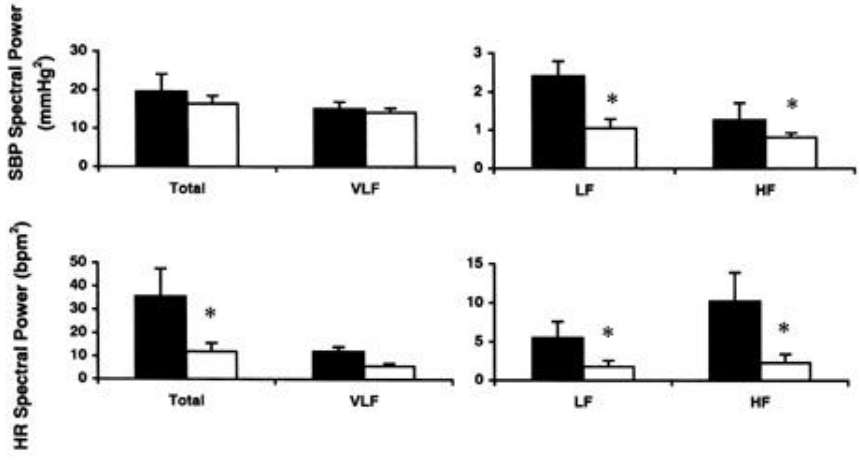

Figure 2—*Spectral powers of sBP and HR in the whole frequency range (Total) and in VLF (0.02–0.07 Hz), LF (0.07–0.14 Hz), and HF (0.25–0.35 Hz) bands in healthy (n = 10) (■) and diabetic (n = 11) (□) subjects.*

Analysis of the gain between sBP and HR

In 10 of the 11 diabetic patients, the baroreflex gain could not be assessed by the *Z* method because *Z* values were too low. The BRS in the remaining patient was lower than the lowest gain value in healthy subjects. Figure 3 represents typical contour-line representation of data obtained from one healthy volunteer and one typical diabetic patient. The number of sequences, selected as representing the baroreflex, was significantly lower for the diabetic patients than the healthy subjects (1573 ± 187 vs. 2189 ± 167, respectively, $P < 0.05$). The BRS determined by the sequence method was lower in the diabetic patients than the healthy subjects, but the difference did not reach statistical significance (Fig. 4).

Spectral analysis found that mean coherence values were lower in diabetic subjects than in the healthy ones in LF

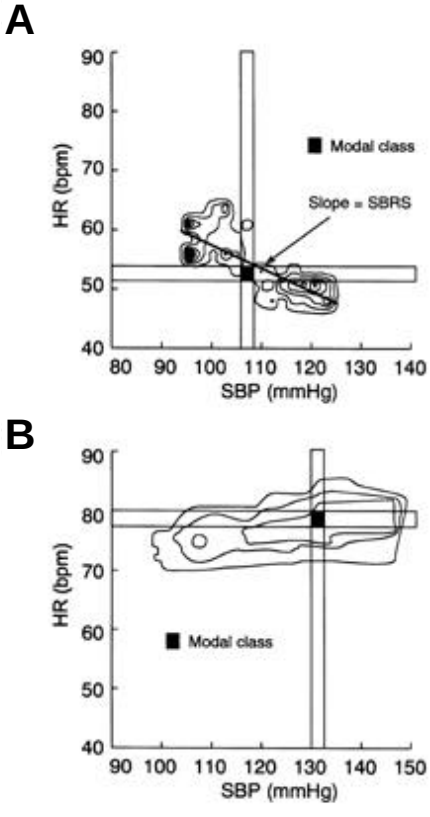

Figure 3—*Contour-line representations of the Z (sBP, HR) values computed on a 1-h recording in one healthy subject (A) and in one diabetic patient (B). Each line joins same Z values with an increment of 0.02. Note that Z values do not exceed 0.06 in this representative diabetic patient (B) and reach 0.18 in this healthy subject (A). SBRS represents the estimated baroreflex gain computed in this healthy subject (A). ■, modal class.*

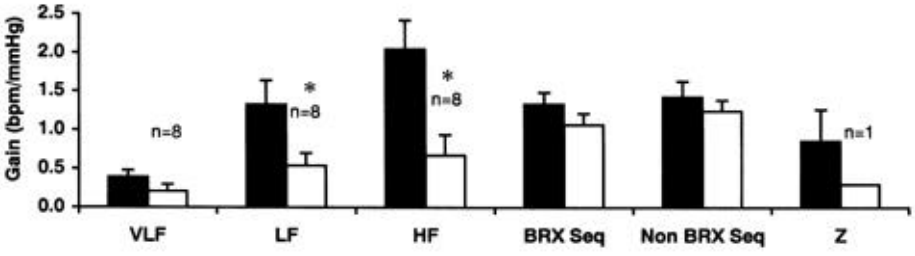

Figure 4—*Baroreflex gain determined by cross-spectral, sequence, and Z methods in healthy (n = 10) (■) and diabetic (n = 11) (□) subjects.*

(0.26 ± 0.03 vs. 0.31 ± 0.02, $P < 0.05$) and HF (0.30 ± 0.03 vs. 0.43 ± 0.04, $P < 0.05$) bands. BRS could be estimated in eight diabetic subjects, but the coherence was too low in the remaining three patients. As shown in Fig. 4, LF and HF gains were significantly lower in diabetic subjects than in healthy subjects. Using the Bonferroni-Dunn test, the BP spectral analyses of the LF and HF bands were the most discriminating indices in diabetic patients (Table 2).

Correlation between Ewing's scores and indices of autonomic nervous activity at rest

These correlations were computed only in diabetic patients (Table 3) because none of the normal volunteers exhibited abnormal responses to the Ewing's tests. Indices of HR variability were significantly correlated with Ewing's scores and with the differences between maximum and minimum HR values during deep breathing. HR fractal dimensions were significantly correlated with the 15:30 ratios of HR after standing up. Total spectral powers of sBP and HR were significantly correlated with the Ewing's scores, with orthostatic sBP variations, and with HR responses during deep breathing (Table 4). In the LF band, sBP and HR spectral powers were correlated with both Ewing's scores and dBP increases during the handgrip test (Table 4). The HF spectral powers of HR were significantly correlated only with Ewing's scores. None of the gains obtained with the analysis of sBP and HR covariations (sequences and cross-spectral methods) were correlated with the Ewing's scores or with absolute values obtained for each test. Only numbers of baroreflex selected sequences were negatively correlated with the Ewing's scores ($r = 0.59$, $P < 0.05$).

CONCLUSIONS — In this study, we have tested four noninvasive methods that are based on mathematical analysis of the spontaneous variations or covariations of sBP and HR to assess the impairment of the autonomic nervous system. These methods that minimized patient collaboration were reported to be more sensitive than clinical tests (23) for diabetic neuropathy. The standard deviation of HR that basically reflected its variability was inversely related to the impairment of the autonomic nervous system. As previously suggested (21), we found that the fractal dimensions of HR were correlated with the global Ewing's scores, with HR variations during deep breathing, and with the 15:30 ratios, which reflect the delay of activation and reaction of the baroreflex regulation. Therefore, both the standard deviation and the fractal dimension of HR, which are global indices of variability, contain information about the degree of impairment of the autonomic nervous system. However, because HR variations during autonomic tests are usually considered to explore more specifically parasympathetic pathways, standard deviation and fractal dimension of HR mainly reflect the parasympathetic activity. On the other hand, BP variability that is modulated by several nervous and humoral factors does not reflect the autonomic impairment.

Fourier analysis gives the measure of the signal periodicity and the relative contribution over a range of frequencies to the global power. The baroreflex loop was reported to be partly responsible for the LF oscillations, which are also modulated by variations in sympathetic nervous activity (8). HF oscillations of sBP have a respiratory origin that is mechanical, but those of HR were reported to be mainly mediated

Table 2—*Standard and critical deviations calculated by Bonferroni test when mean values were significant between groups*

	Standard deviation	Critical deviation	Difference (%)
LF spectral power (sBP)	1.4	0.6	57
HF spectral power (sBP)	0.91	0.41	55
Number of sequences	370	167	54
HR fractal dimension	0.18	0.12	33
sBP fractal dimension	0.19	0.14	26
LF spectral gain	1.1	1.0	9
HF spectral gain	1.1	1.0	9
HF spectral power (HR)	8	7.8	2.5
HR power spectrum	23.6	23.4	1
LF spectral power (HR)	4.02	4.01	0.2

To classify the relative sensitivities of the methods, differences between critical and standard deviations are expressed as percentage of the mean deviation.

Table 3—*Spearman's rank coefficient correlation between indices of BP and HR variabilities (1-h sBP and HR standard deviation and fractal dimension) and indices obtained during Ewing's tests in diabetic subjects*

	Standard deviation		Fractal dimension	
	sBP	HR	sBP	HR
Ewing's score	−0.31	−0.70*	−0.49	−0.78*
Δ sBP (standing up)	−0.23	−0.52	−0.05	−0.25
15:30 ratio	0.08	0.02	0.43	0.68†
HR min − max (deep breathing)	−0.15	0.82*	−0.20	0.64†
HR min/max (Valsalva)	−0.12	0.35	−0.01	−0.23
Δ dBP (handgrip)	0.24	0.49	−0.23	0.14

$n = 11$. *$P < 0.01$; †$P < 0.05$.

Table 4—*Spearman's rank coefficient correlation between sBP and HR spectral power in LF (0.07–0.14 Hz) and HF (0.25–0.35 Hz) bands and indices obtained during Ewing's tests in diabetic subjects*

	Total spectral power		LF spectral power		HF spectral power	
	sBP	HR	sBP	HR	sBP	HR
Ewing's score	−0.59*	−0.57*	−0.62*	−0.65†	−0.52	−0.68†
Δ sBP (standing up)	−0.71†	−0.67*	−0.22	−0.30	−0.57	−0.30
15:30 ratio	0.45	0.43	0.39	0.49	0.30	0.45
HR min − max (deep breathing)	0.64*	0.60*	0.49	0.43	0.48	0.43
HR min/max (Valsalva)	0.01	0.20	0.40	0.48	0.42	0.30
Δ dBP (handgrip)	0.14	0.24	0.59*	0.60*	0.53	0.53

$n = 11$. *$P < 0.05$; †$P < 0.01$.

by a vagal activation. Spectral analysis could then provide a sensitive and quantitative approach for early diagnosis of autonomic neuropathy (7,24). Unfortunately, the information provided by the different frequency bands has never been specifically established. In our study, the total spectral power and the spectral power in the LF and HF bands of both sBP and HR were significantly lower in diabetic subjects. The total powers of sBP and HR were significantly negatively correlated to Ewing's scores, to sBP decrease after standing up unaided, and to HR response during deep breathing. Our results confirmed that total spectral power is related to global autonomic dysfunction in diabetic patients. Furthermore, since LF-HR and LF-sBP spectral powers were correlated to Ewing's scores and to dBP increases during the handgrip test, the major contribution of these oscillations to the sympathetic component was confirmed (25). Therefore, sBP and HR spectral indices reflected in a similar way the impairment of the autonomic nervous system. Spectral analysis of sBP in LF and HF bands appeared to be the most discriminating parameter (Table 2), confirming that beat-to-beat sBP recording could detect diabetic neuropathy (22).

The cardiac baroreflex component of the autonomic nervous system can be analyzed by the study of the sBP and HR covariations. Three methods to assess the BRS, which rely on very different principles, were validated in humans (11,20,22). The *Z* method, which relies on the statistical dependence between sBP and HR, separated diabetic from healthy subjects well but it was unable to determine the BRS in 10 of the 11 diabetic patients. This threshold behavior is a limitation of the *Z* method to determine the BRS in patent neuropathy. However, the sensitivity of the method has already been demonstrated to detect a slight baroreflex impairment in rats (26) and in hypertensive humans (27). In our study, the *Z* method might be too sensitive in our diabetic patients with nonsymptomatic orthostatic hypotension. Spectral gains in the LF and HF bands could be computed in 8 of the 11 diabetic subjects and were lower than in healthy volunteers. The small number of subjects and the reduced confidence in calculated gains (decreased coherence values) may explain the lack of correlation with the clinical test indices. Moreover, the autonomic conduction rate that is decreased in diabetic neuropathy (28) may delay the baroreflex regulatory frequencies. Thus, LF and HF bands may not reliably describe the BP regulation in diabetic subjects. The sequence method selected short sequences of at least three consecutive beats with a baroreflex pattern (variations of sBP and HR in opposite directions). In diabetic patients, the number of baroreflex selected sequences was lower than that in healthy subjects. These numbers of baroreflex sequences that were correlated with the Ewing's scores could reflect the diabetic neuropathy impairment. The baroreflex gain estimated with the sequence method was not significantly altered. The large interindividual variability of the sequence BRS, which weakened its physiological significance, may explain the lack of difference between groups.

In conclusion, cardiovascular diabetic neuropathy can be reliably assessed during a beat-to-beat BP recording under resting conditions. Mathematical methods that aimed to analyze BP or HR variabilities gave information similar to the Ewing's scores. Among them, spectral sBP analysis was the most sensitive one for confirming diabetic neuropathy. These methods can, furthermore, provide specific information on the cardiac baroreflex. *Z* and spectral analyses of the baroreflex separated diabetic from healthy subjects well. For incipient neuropathy, these methods that should be able to compute BRS could enhance clinical interest in *Z* and spectral analyses.

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