ELSEVIER

International Journal of Cardiology 104 (2005) 307–313

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Comparison of fast Fourier transform and autoregressive spectral analysis for the study of heart rate variability in diabetic patients

Denis Chemla*, Jacques Young, Fabio Badilini, Pierre Maison-Blanche, Hélène Affres, Yves Lecarpentier, Philippe Chanson

Service de Physiologie Cardio-Respiratoire and Service d'Endocrinologie, Centre Hospitalo-Universitaire de Bicêtre, Assistance Publique-Hopitaux de Paris, Université Paris Sud 11, 78 rue du Général Leclerc, 94 275 Le Kremlin Bicêtre, France
Unité Propre de l'Enseignement Supérieur 2705, Université Paris-Sud 11, 92 141 Clamart, France

Received 8 June 2004; received in revised form 13 September 2004; accepted 7 December 2004
Available online 21 February 2005

Abstract

Introduction: Impaired heart rate variability (HRV) is associated with poor outcome in diabetic patients. The present prospective study compared spectral components of HRV obtained by either fast Fourier transform (FFT) or autoregressive (AR) analyses in diabetic patients.
Methods: Thirty patients (49±12 years; 11 F/19 M; 60% with insulin-dependent type 1 diabetes) underwent 24-h ambulatory electrocardiographic recordings which comprised a 10-min resting period at the onset (n=30) and end (n=12) of the monitoring. Spectral analysis was applied to 5-min sequences at rest, and the total power and power spectra integrated over the very low (VLF), low (LF), and high (HF) frequency bands were obtained.
Results: Fifteen patients had moderately depressed HRV and two patients had highly depressed HRV (standard deviation of the RR intervals over 24-h<100 ms and <50 ms, respectively). Both raw data and ln-transformed data were significantly different between FFT and AR. All spectra component were obtained in each patient using FFT. Using AR, the LF/HF ratio could not be estimated or was zero in 4 and 11 patients, respectively. The AR results were more sensitive than FFT results to minor changes (±5%) in the timing of the onset of analysis. The day-to-day reproducibility of FFT was better than that of AR. Finally, using FFT, the LF/HF ratio, LFnu, and HFnu were essentially redundant (nu=normalized units).
Conclusions: The spectral components of short-term HRV calculated by using the FFT and AR methods were not interchangeable and FFT analysis must be preferred in diabetic patients.

Keywords: Heart rate; Autonomic tone; Autonomic neuropathy

1. Introduction

Cardiovascular autonomic neuropathy is a complication of diabetes which results from damage to the autonomic nerve fibers that innervate the heart and blood vessels, thus leading to decreased heart rate variability (HRV) and abnormal blood pressure control. Indexes of HRV are useful to detect the early impairment in autonomic tone at a time when dysautonomia is not yet clinically patent [6,15,35]. The critical evaluation of HRV tests is therefore important if one considers: i) the high incidence of diabetes in the normal population; ii) the high incidence (~20%) of abnormal cardiovascular autonomic function in diabetes; and iii) the association between impaired HRV and increased risk of life-threatening cardiovascular events in these patients [7,16,35].

Two HRV methods are most often applied, namely bedside tests and the 24-h ambulatory electrocardiogram. The complete battery of classic autonomic tests is of great value but is long to perform and requires good cooperation from the patient, and it only examines short-term HRV in the time-domain [16]. As the 24-h ambulatory ECG

* Corresponding author. Tel.: +331 45 21 25 63; fax: +331 45 21 37 78.
E-mail address: denis.chemla@bct.ap-hop-paris.fr (D. Chemla).

0167-5273/$ - see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2004.12.018

examines both short-term and long-term HRV in both the time- and frequency-domain, this simple and sensitive method is increasingly used in diabetic patients [5]. The recommendation to use standardized duration of recordings for HRV assessment has been proposed to enable comparisons of research studies [34]. The 24-h standard deviation of normal RR intervals (SDNN) provides a simple and sensitive scale of cardiovascular risk, while the spectral analysis of HRV over 5 min helps to quantify the sympathovagal balance alterations which play an important role in the pathophysiology and prognosis of the disease [23,25,34].

In the frequency-domain, HRV is described as the sum of elementary oscillatory components defined by their frequency and amplitude (power). Physiological mechanisms responsible for power components cannot be considered stationary during the 24-h period, and short-term analyses under controlled conditions are therefore recommended (i.e., 5 min at rest) [34]. Two spectral methods can be used, namely the fast Fourier transform (FFT) [2] and the autoregressive (AR) methods [19,25,28]. Spectral frequency components are either integrals of power spectrum density over specific bands (FFT) or components automatically determined by autoregressive algorithms (AR). As recently pointed out, a study comparing the two methods is important for the proper interpretation of spectral data in terms of physiologic and pathologic processes [22], and previous studies have compared the two methods in healthy subjects [3,29] and in hypertensives [4]. In diabetic patients, both the FFT method [8–11,20,21,36] and the AR method [6,7,13,31,32] have been used, but up to now no study has compared the results of the two methods.

The aim of the present study was to compare short-term spectral HRV measurements obtained by FFT and AR methods in diabetic patients. We tested whether or not the two methods provide interchangeable estimates of spectral HRV in diabetic patients.

2. Material and methods

2.1. Study population

The subjects included in this prospective study were diabetic patients hospitalized in our diabetes care unit. Informed consent was obtained for each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institution's human research committee. Patients with known cardiovascular diseases or rhythm disturbances were excluded from the study and all patients were free of any cardiovascular medication. Thirty diabetic subjects aged 49±12 years, 19 men and 11 women, 18 with insulin-dependent type 1 diabetes and 12 with non-insulin dependent type 2 diabetes, were recruited consecutively. Neurological status and autonomous nervous system status were assessed by a physician unaware after the HRV results. Sixteen patients had peripheral neuropathy and four patients had clinical signs of dysautonomia.

2.2. Data acquisition and analysis

Ambulatory electrocardiographic recordings were acquired with a dual-lead analog Holter recorder (SEER, Marquette-Helige, GE Medical Systems, Velizy, France). Holter was positioned in the morning. A 10-min resting period was performed at the onset of the recording period in all patients. In a subset of twelve patients, a 10-min resting period was also performed at the end of the recording period in order to test the day-to-day reproducibility of the measurements. Patients were instructed to behave in a normal manner during 24 h. Analog data were digitized at 200 Hz and edited by a cardiologist on a Mars 8000 Laser Holter station (Marquette-Helige, GE Medical Systems, Velizy, France). The validation procedure consisted of beat labeling and tagging of noisy regions. Both ECG raw data and annotation were transferred to a personal computer for dedicated HRV analysis [3,4]. In an attempt to rule out the hypothesis that potential differences between FFT and AR results would be due to technical limitations or specific features of the Holter recordings, only sinus rhythm, high-quality recordings were selected for entering the final analysis. Exclusion criteria related to recording characteristics included: noisy regions with absence of at least one good quality lead (n=11), >2% ectopic beats or ectopic beats occurring during the 10-min resting period (n=9), a duration <24 h (n=1), previously unrecognized atrioventricular block (n=1), and movements during the resting period (n=1).

2.3. Heart rate and heart rate variability

Time- and frequency-domain HRV variables were calculated as previously described [3,4]. Time-domain variables included: mean sinus heart rate (HR), average RR interval (NN), standard deviation of the RR intervals (SDNN), percentage of normal consecutive RR intervals differing by >50 ms (pNN-50), and root mean of squared successive differences (RMSSD). From a theoretical point of view, spectral analysis requires rigorous stationary conditions which are unknown to biology and medical science [23]. Short-term analyses under controlled conditions are therefore recommended, and it is now admitted that the analysis of 5-min resting ECG offers a reasonable, practical compromise [22,34]. Editing of the tachograms may also help eliminate the runs with step changes of major trends in the tachogram [23,34], as performed in the present study. The FFT power spectra were calculated with the method of average periodogram, also called the Walch periodogram, as previously described [3,4] and recommended [34]. The AR power spectra were obtained as

Table 1
Time domain heart rate variability parameters at rest over a 5-min period (n=30)

	Mean±S.D.	Range
NN (ms)	822±127	600–1120
SDNN (ms)	31±24	5–125
pNN-50 (%)	6±13	0–53
RMSSD (ms)	25±27	6–145

NN: normal RR intervals. SDNN: standard deviation of the RR intervals. pNN-50: percentage of normal consecutive RR intervals differing by>50 ms. RMSSD: root mean of squared successive differences.

previously described [3,4]. In brief, identification of the model was achieved with a recursive Levinson–Durbin algorithm for the determination of model parameters [19] and Akaike criterion for the choice of model order [1]. The frequency-domain variables included the total power (TP) spectrum (0 to 0.4 Hz) and the power spectra integrated over very low frequency (VLF, 0 to 0.04 Hz), low-frequency (LF, 0.04 to 0.15 Hz), and high-frequency (HF, 0.15 to 0.4 Hz) bands.

It is widely believed that i) the HF power reflects vagal modulation of the heart rate; ii) both the LF power and the LF/HF ratio reflect a complex interplay between sympathetic and parasympathetic modulation of heart rate; and iii) the physiological meaning of the VLF power assessed from short-term recordings (~5 min) is less defined and its interpretation is not recommended when discussing power spectra density results [34]. In the present study, the LF/HF ratio was used to quantify the sympathovagal balance, as previously proposed [23–26,28,34], although it must be noted that there is still an active debate about the exact physiological meaning of LF, HF, and the LF/HF ratio [14,15,22,27].

Measurements of LF and HF components were made in absolute values of power (ms^2) and in normalized units (nu, in %) which represent the relative value of each power component in proportion to the total power minus VLF component. Finally, log-transformed values were also calculated to normalize the distribution.

2.4. Statistical analysis

Data are presented as means±S.D. Time-domain parameters were calculated over the 24-h period. Both time-domain and frequency-domain parameters were also calculated over 5 min during the resting periods performed at the onset and end of the recordings. At the baseline, differences between FFT and AR methods were studied i) by using paired t test; ii) by calculating the mean bias [100×(AR−FFT)/(AR+FFT)/2]. The influence of mild changes in the onset of the analysis was tested by varying by 5% (15 msec) the onset of analysis. We studied the first 5-min resting period at the onset of the monitoring (n=30). We studied three overlapping 5-min resting periods spaced out ±15 sec apart from the reference $T0$ period, namely $T0-15$ sec, T0 and T0+15 sec. Coefficient of variation was calculated as [(S.D./mean)×100]. The measurements at onset and end of the recording (n=12) were compared using paired t test and calculation of the mean bias. A P value<0.05 was considered statistically significant.

3. Results

The results of the time-domain analysis at baseline are given on Table 1. Using published 24-h SDNN cutoffs of moderately depressed HRV (50 to 100 ms) and highly depressed HRV (<50 ms) [34], 15 patients (50%) had moderately depressed HRV and 2 patients (7%) had highly depressed HRV (Fig. 1). The FFT and AR results obtained during the 5-min resting period at the onset of the recording are given on Table 2. With the exception of HF, frequency-domain variables were not interchangeable when FFT and AR methods were compared. Major differences were observed between FFT and AR mean results and the mean bias was huge for each frequency-domain variable but HF (Table 2). Similar results were obtained when log-transformed values were considered.

All spectral components were obtained in each patient using the FFT method. Conversely, using the AR method, there were several null or missing values for LF and HF. In twelve patients, the power spectra integrated over the low-frequency band was null, thus resulting in a null LF/HF ratio. In one patient, the power spectra integrated over the high-frequency band was null such that it was not possible

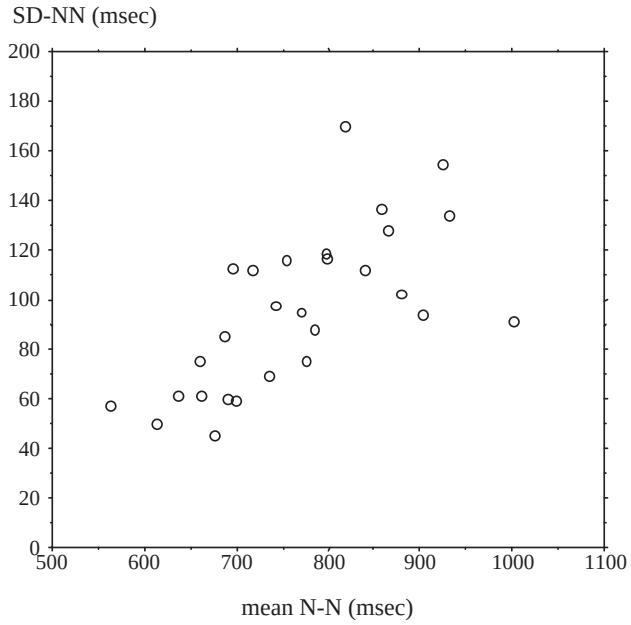

Fig. 1. Individual values for 24-h-mean NN and 24-h SDNN in the study population (n=30). 15 patients had moderately depressed heart rate variability and 2 patients had highly depressed heart rate variability (24-h SDNN ranging from 50 to 100 ms and <50 ms, respectively).

Table 2
Comparison between fast Fourier transform (FFT) and autoregressive (AR) methods at baseline

	FFT	AR	*P* value
TP (ms^2)	958±1589	1270±2201	0.05
VLF (ms^2)	113±217	442±490	0.0002
LF (ms^2)	364±439	222±428	0.05
HF (ms^2)	348±1113	485±1579	0.18
ln-TP	5.98±1.43	6.30±1.35	0.0001
ln-VLF	4.64±1.46	5.40±1.41	0.0001
ln-LF	5.50±1.04	5.02±1.54	0.0103
ln-HF	4.35±1.75	4.54±1.72	0.0001
LFnu (%)	61±22	32±32	0.0001
HFnu (%)	31±18	54±26	0.0001
LF/HF (–)	3.20±2.57	1.12±1.60	0.0003

Values are means±S.D. FFT: fast Fourier transform method. AR: autoregressive method. TP: total power. VLF: very-low frequency band. LF: low-frequency band. HF: high-frequency band. nu: normalized units.

to calculate the LF/HF ratio. It was not possible to compute any value for LF in one patient, for HF in one patient and for both HF and LF in one patient. Similar results were obtained when various fixed model order values were imposed. When only the patients with a complete data-set were considered (i.e., with non-zero LF, HF, and LF/HF values using the AR method; n=15), same results as those observed in the overall population were obtained when FFT and AR were compared.

When the onset of analysis was modified by ±5%, the 5-min time-domain variables of HRV appeared stable, as attested to by the low coefficient of variation of NN (0.2±0.1%), SDNN (3±5%), pNN50 (5±7%), and RMSSD (3±6%). The 5-min frequency-domain FFT variables were also poorly modified (Table 3). Conversely, using the AR method, both LF the LF/HF ratio appeared extremely sensitive to initial conditions of the analysis, as attested to by their 47% and 44% coefficient of variation, respectively (Table 3).

Over the first 5-min resting period, the SDNN was positively related to FFT indices, especially TP, as expected (R=0.94; P<0.001). The SDNN was also related to HF (R=0.81) and LF (R=0.80; each P<0.001) but no the LF/HF ratio. Using multivariate analysis, TP and HF explained

Table 3
Short-term stability of frequency-domain heart rate variability parameters at rest using the moving average analysis

	FFT	AR	*P* value
Cvar-TP (%)	8±5	7±9	0.38
Cvar-VLF (%)	13±11	13±15	0.76
Cvar-LF (%)	10±6	47±55	0.0044
Cvar-HF (%)	5±3	6±6	0.49
Cvar-(LF/HF) (%)	10±5	44±55	0.0115

Stability was tested at rest by analyzing three overlapping 5-min periods spaced out ±15 sec apart from the reference $T0$ period (T−15 sec; $T0$; T+15 sec; see Methods). Coefficients of variation (Cvar) are expressed as percentages and mean±S.D. values are given. FFT: fast Fourier transform method. AR: autoregressive method.

Table 4
Day-to-day reproducibility of fast Fourier Transform (FFT) and autoregressive (AR) variables (n=12)

	Onset of the 24-h recording	End of the 24-h recording	*P* value	Mean bias %±S.D.
NN (msec)	783±113	770±155	0.63	2±11
SDNN (msec)	30±31	21±11	0.31	17±41
LF/HF (–) using FFT method	3.50±3.17	3.04±2.09	0.53	2±74
LF/HF (–) using AR method	0.96±1.67	2.72±3.80	0.20	102±105

NN: normal RR intervals. SDNN: standard deviation of the RR intervals. LF: low-frequency band. HF: high-frequency band.

92% of the variability of SDNN, while LF and the LF/HF ratio had not significant additional value.

In a subset of 12 patients, the 5-min recordings were analyzed both at onset and end of the Holter. The day-to-day reproducibility was good for time-domain variables (mean bias ranging from 2% to 17%), was mild-to-moderate for frequency-domain FFT variables (mean bias ranging from 2% to 39%), while reproducibility was poor for frequency-domain AR variables (mean bias ranging from −27% to 102%). The LF/HF ratio obtained by using the FFT method appeared more reproducible than that obtained by using the AR method (Table 4).

At baseline, using the FFT method, the sum of the LF and HF spectral components was <80% of the total power minus VLF difference in only two patients (50% and 64%, respectively), thus indicating a significant spectral component >0.40 Hz. In the remaining 28/30 patients, the sum of the LF and HF spectral components encompassed for 94±5% of the total power minus VLF difference. As a result, LFnu, HFnu, and the LF/HF ratio were essentially redundant in these patients (Fig. 2).

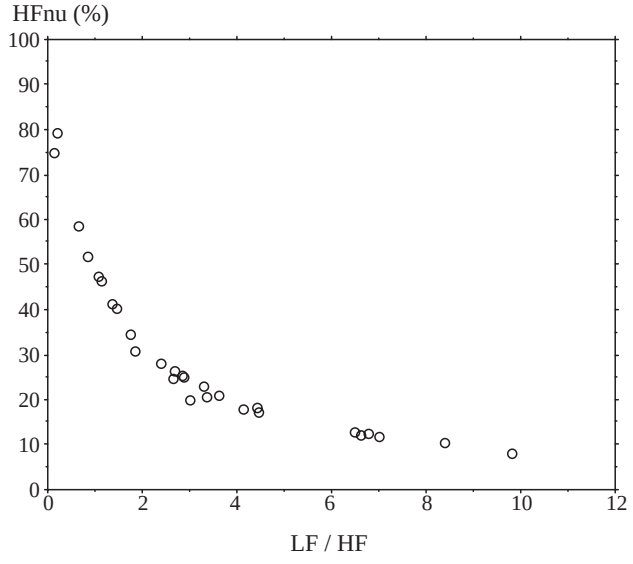

Fig. 2. Relationship between HFnu (%) and the LF/HF ratio.

4. Discussion

Impaired heart rate variability is associated with poor outcome in diabetic patients, and the ambulatory electrocardiogram is increasingly used to precisely quantify the HRV of diabetic patients in the time- and frequency-domain. Given the high incidence of diabetes and the high incidence of abnormal cardiovascular autonomic function in diabetes, it is important to critically evaluate the two spectral methods currently used. The present prospective study indicated that the fast Fourier transform and autoregressive analyses provide significantly different estimates of heart rate variability in resting diabetic patients. The spectral components of HRV calculated by using the two methods were not interchangeable and the FFT analysis must be preferred to AR for the following reasons: i) all spectra components were obtained in each patient using FFT while numerous null or missing values were obtained using the AR method; ii) the AR results were more sensitive than FFT results to minor changes ($\pm$5%) in the timing of the onset of analysis; iii) the day-to-day reproducibility of FFT was better than that of AR. Finally, by applying FFT over a 5-min resting period, the LF/HF ratio and LFnu and HFnu (nu=normalized units) were essentially redundant in diabetic patients.

Significant differences between raw powers obtained by using FFT and AR analyses have been reported in healthy [3] and hypertensive [4] subjects. Differences in quantitative results are explained by the mode of spectrum integration of each spectral approach [3,4,29]. The present study extends these findings to diabetic patients at rest, in whom the low- and high-frequency components obtained by the two methods as well as their ratio (LF/HF) may have a different physiological interpretation. Spectral data were analyzed over a 5-min resting period, as recommended [22,34]. All spectra components were obtained in each patient using FFT, such that it was always possible to calculate the LF/HF ratio. In hypertensive subjects, we have previously reported the possibility of missing LF and HF data using the AR method [4]. Consistently, using the AR method in diabetics, it was not possible to calculate the LF/HF ratio in four patients given the lack of LF and HF spectral components. Furthermore, the LF/HF was zero in eleven patients. Overall, a zero- or missing-value for the LF/HF ratio was found in 50% patients. Although controversial [14,27], this ratio is currently used to precisely quantify the so-called sympathovagal balance [24–26,28]. In both the entire study population and the 15 patients with complete data-set, the LF/HF ratio significantly differed between the AR and FFT methods, thus also confirming previous studies on healthy [29] and hypertensive subjects [4].

The reproducibility of short-term frequency-domain HRV measurements has been questioned. In normal subjects, Pitzalis et al. have shown that both FFT and AR spectra were poorly reproducible when evaluated from short-term recordings in eighteen normal volunteers [29]. It has been suggested that patients with decreased HRV may have a higher reproducibility of spectral indices than healthy subjects [18,29,33] although conflicting results have been published in diabetic subjects [9,17,30]. In our study involving 57% patients with moderately-to-highly depressed HRV, the day-to-day reproducibility of 5-min time-domain HRV indices was good, the day-to-day reproducibility of FFT was moderate, and that of AR was weak. Importantly, FFT was less sensitive than AR to minor changes in the timing of onset of the analysis.

Overall, our results confirmed in diabetic patients that the two methods were not interchangeable and indicated that the AR analysis may be unreliable in these patients. Indeed, we feel that the unusually high frequency of zero- or missing-values, the low day-to-day reproducibility and marked sensitivity to small changes in the onset of analysis make it impossible to recommend the current use of the AR method in diabetic patients. Consistently, the uncertainty of the AR estimates has been previously pointed out in a theoretical study concluding that one must be careful in assigning pathophysiological origins to specific features of the AR spectral components [12].

Because the AR analysis is one of the methods currently used to quantify HRV in numerous diseased populations including diabetic patients, the reasons explaining our results must be discussed. From a theoretical point of view, the uncertainty of AR estimates appears related to the method per se rather than to the cardiovascular field of application, as the weakness of the AR analysis is not specific to heart rate data [12]. The role of model order and phase dependency must be discussed. In our study, the percentage of missing AR data did not decrease by increasing the model order. The phase dependency of AR results [12,19] may be involved, as suggested by the strong influence of small changes in the onset of analysis on the results in our study. Differences in the way the power within a band is computed may also be involved (tail effect), as previously proposed by Badilini et al. [3]. Indeed, with FFT, the power is calculated by integration of the spectrum between the band lower and upper limits. Conversely, with AR, the criteria of assignment are based on the central frequency value of a well-defined oscillatory pattern, such a peak being not always observed. Furthermore, when two neighboring components are considered, the tails of each component could be assigned to one or another band depending on the method used [3]. Other limitations related to more complex mathematical characteristics of the AR method may be also involved [3,4,12,19,29].

Although the FFT method must be preferred, we also observed moderate day-to-day reproducibility and moderate sensitivity to the timing of onset of the analysis for FFT spectra. As a result, our study suggests that FFT data must be interpreted with caution and in light of other indices quantifying the sympathovagal balance, namely time-domain HRV indices. Indeed, although time-domain and FFT frequency-domain indices of HRV were strongly related, only time-domain indices exhibited excellent day-

to-day reproducibility and remained nearly unchanged when the onset of analysis was modified by ±5%.

The present study demonstrated major redundancy between LFnu, HFnu, and the LF/HF ratio in resting diabetics patients studied by applying FFT to 5-min tachograms (nu=normalized units). Normalization is performed by dividing LF and HF by the total power minus VLF power difference. In our study, the VLF component was negligible in 93% of the patients and one mathematical implication was that LF/HF, LFnu, and HFnu were essentially redundant in our study population. Such a redundancy has been previously stressed by Eckberg [14], on the basis of its retrospective analysis of published data [28,34], and this was viewed as a major limitation of the sympathovagal concept [14,15]. Malliani and colleagues also discussed the possibility of such a redundancy but this was viewed as a strength rather than a weakness of the spectral approach of the sympathovagal balance [26].

The limitations of our study must be discussed. First, our population may be only representative of that of an in-hospital diabetes department, especially in terms of data reproducibility. Using published 24-h SDNN cutoffs of HRV [34], 13 patients (43%) had normal HRV, 15 patients (50%) had moderately depressed HRV, and 2 patients (7%) had highly depressed HRV. Second, our results may not apply to populations other than diabetic patients with no overt cardiovascular disease. Patients with known cardiovascular disease and patients who were given cardiovascular drug therapy were excluded from the final analysis. We cannot exclude the possibility that part of our study population may have suffered from silent myocardial ischemia as no diagnostic work-out was systematically performed in order to rule out this hypothesis. Third, the redundancy between LF/HF, LFnu, and HFnu may not apply to spectral methods other than FFT, to other populations than diabetic patients, and to other conditions than 5-min rest. Indeed, using AR in healthy subjects, Malliani et al. observed that LFnu and HFnu were not redundant as i) the sum LFnu and HFnu falls short of 100% given the presence of smaller components; and ii) three variables, namely RR, LFnu, HFnu, concentrate the information contained in the entire spectra during postural changes [24]. Finally, in healthy and hypertensive subjects, the dynamic trends provided by the FFT and AR methods were consistent following either passive tilt test or beta-adrenoceptor blockade [3,4], thus implying that the two methods are valuable in populations other than diabetic patients, and under dynamic conditions.

In conclusion, our Holter study indicates that short-term heart rate variability was reliably assessed by both time-domain and FFT frequency-domain indices in diabetic patients, while the autoregressive spectral analysis was unreliable. Standardization of HRV spectral analysis may help improve the diagnosis of abnormal cardiovascular autonomic function in diabetes, a point that deserves further studies.

References

[1] Akaike H. A new look at the statistical model identification. IEEE Trans Autom Cont 19:716–23.
[2] Akselrod S, Gordon D, Ubel FA, Shannon DC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213:220–2.
[3] Badilini F, Maison-Blanche P, Coumel P. Heart rate variability in passive tilt test: comparative evaluation of autoregressive and FFT spectral analyses. PACE 1998;21:1122–32.
[4] Badilini F, Maison-Blanche P, Champomier P, Provost JC, Coumel P, Milon H. Frequency-domain heart rate variability in 24-hour Holter recordings: role of spectral method to assess circadian patterns and pharmacological autonomic modulation. J Electrocardiol 2000;33:147–57.
[5] Bellavere F. Heart rate variability in patients with diabetes and other noncardiological diseases. In: Malik M, Camm AJ, editors. Heart Rate Variability. Armonk Futura Publishing Co. Inc.; 1995. p. 507–16. Chapt. 38.
[6] Bellavere F, Balzani I, de Masi G, Carraro M, Carenza P, Cobelli C, et al. Power spectral analysis of heart rate variations improves assessment of diabetic care autonomic neuropathy. Diabetes 1992;41:633–40.
[7] Bernardi L, Ricordi L, Lazzari P, Solda P, Calciati A, Ferrari MR, et al. Impaired circadian modulation of sympathovagal activity in diabetes. A possible explanation for altered temporal onset of cardiovascular disease. Circulation 1992;86:1443–52.
[8] Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation 1993;88:927–34.
[9] Burger AJ, Charlamb M, Weinrauch LA, d'Elia J. Short- and long-term reproducibility of heart rate variability in patients with long-standing type I diabetes mellitus. Am J Cardiol 1997;80:1198–202.
[10] Burger AJ, d'Elia JA, Weinrauch LA, Lerman I, Gaur A. Marked abnormalities in heart rate variability are associated with progressive deterioration of renal function in type I diabetic patients with overt nephropathy. Int J Cardiol 2002;86:281–7.
[11] Carnethon MR, Lia D, Evans GW, Cascio WE, Chambless LE, Heiss G. Correlates of the shift in heart rate variability with an active postural change in a healthy population sample: the atherosclerosis risk in communities study. Am Heart J 2002;143:808–13.
[12] Christini DJ, Kulkarni A, Rao S, Stutman ER, Bennett FM, Hausdorff JM, et al. Influence of autoregressive model parameter uncertainty on spectral estimates of heart rate dynamics. Ann Biomed Eng 1995;23:127–34.
[13] Comi G, Sora MG, Bianchi A, Bontempi B, Gianoglio P, Cerutti S, et al. Spectral analysis of short-term heart rate variability in diabetic patients. J Auton Nerv Syst 1990;30:S45–9.
[14] Eckberg DL. Sympathovagal balance. A critical appraisal. Circulation 1997;96:3224–32.
[15] Eckberg DL. Response to correspondences on "sympathovagal balance a critical appraisal". Circulation 1998;98:2643–4.
[16] Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. Q J Med 1980;193:95–108.
[17] Gerritsen J, Dekker JM, TenVoorde BJ, Kostense PJ, Heine RJ, Bouter LM, et al. Impaired autonomic function is associated with increased mortality, especially in subjects with diabetes, hypertension, or a history of cardiovascular disease. Diabetes Care 2001;24:1793–8.
[18] Kautzner J, Hnatkova K, Staunton A, Camm AJ, Malik M. Day-to-day reproducibility of time-domain measures of heart rate variability in survivors of acute myocardial infarction. Am J Cardiol 1995;76:309–12.
[19] Kay SM, Marple SL. Spectrum analysis: a modern perspective. Proc IEEE 1981;69:1380–419.
[20] Laitinen T, Vauhkonen IKJ, Niskanen LK, Hartikainen JE, Lansimies EA, Uusitupa MI, et al. Power spectral analysis of heart rate variability

during hyperinsulinemia in nondiabetic offspring of type 2 diabetic patients. Diabetes 1999;48:1295–9.
[21] Liao D, Carnethon M, Evans GW, Cascio WE, Heiss G. Lower heart rate variability is associated with the development of coronary heart disease in individuals with diabetes. The atherosclerosis risk in communities (ARIC) study. Diabetes 2002;51:3524–31.
[22] Malik M. Sympathovagal balance: a critical appraisal. Circulation 1998;98:2643.
[23] Malliani A. The pattern of sympathovagal balance explored in the frequency domain. News Physiol Sci 1999;14:111–7.
[24] Malliani A, Pagani M, Furlan R, Guzetti S, Lucini D, Montano N, et al. Individual recognition by heart rate variability of two different autonomic profiles related to posture. Circulation 1997;96:4143–5.
[25] Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991;84: 482–92.
[26] Malliani A, Pagani M, Montano N, Mela GS. Sympathovagal balance: a reappraisal. Circulation 1998;98:2640–2.
[27] Malpas SC. Neural influences on cardiovascular variability: possibilities and pitfalls. Am J Physiol, Heart Circ Physiol 2002;282:H6–20.
[28] Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178–93.
[29] Pitzalis MV, Mastropasqua F, Massari F, Forleo C, Di Maggio M, Passantino A, et al. Short- and long-term reproducibility of time and frequency domain heart rate variability measurements in normal subjects. Cardiovasc Res 1996;32:226–33.
[30] Sinnreich R, Kark JD, Friedlander Y, Sapoznikov D, Luria MH. Five minute recordings of heart rate variability for population studies: repeatability and age–sex characteristics. Heart 1998;80:156–62.
[31] Spallone V, Bernardi L, Maiello MR, Cicconetti E, Ricordi L, Fratino P, et al. Twenty-four-hour pattern of blood pressure and spectral analysis of heart rate variability in diabetic patients with various degrees of autonomic neuropathy. Comparison to standard cardiovascular tests. Clin Sci (Lond) 1996;91:105–7.
[32] Spallone V, Bernardi L, Ricordi L, Solda P, Maiello MR, Calciati A, et al. Relationship between the circadian rhythms of blood pressure and sympathovagal balance in diabetic autonomic neuropathy. Diabetes 1993;42:1745–52.
[33] Stein PK, Rich MW, Rottman JN, Kleiger RE. Stability of index of heart rate variability in patients with congestive heart failure. Am Heart J 1995;129:975–81.
[34] Task force of the ESC and NASPE. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Eur Heart J 1996;17:354–81.
[35] Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553–79.
[36] Whang W, Bigger JT. Comparison of the prognostic value of RR-interval variability after acute myocardial infarction in patients with versus those without diabetes mellitus. Am J Cardiol 2003;92: 247–51.