Frequency-domain Heart Rate Variability in 24-Hour Holter Recordings: Role of Spectral Method to Assess Circadian Patterns and Pharmacological Autonomic Modulation

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Abstract: Different spectral methodologies for heart rate variability were recently shown to provide the same qualitative results in the context of passive tilt test. However, the impact of the method and the use of normalized power units in long-term ECG monitoring is still debated. Autoregressive and Fast Fourier transform (FFT) spectral approaches were applied to assess circadian modulation and the effect of beta-blocker administration in mild hypertensive patients who underwent continuous ambulatory ECG recording (n = 44, 51 ± 12 years, 30 men). Spectral analysis was applied to 5-minute sequences and spectral parameters representative of each circadian period (24 hour, day, night) were calculated. In baseline recordings, FFT spectral method provided a smaller estimate of total and very low frequency powers. On the contrary, low- and high-frequency components were systematically larger with FFT. Circadian variations were in favor of an increased overall nocturnal variability but of a reduced low frequency normalized power with both spectral methods. Chronic oral administration of beta-blocker induced an increase of all spectral components except for an unchanged low-frequency normalized power, independently from the spectral approach. In spite of quantitative differences, the qualitative assessment of circadian patterns and beta-blockade effect by autoregressive- and FFT-based spectral analyses is equivalent. The low-frequency component of heart rate variability cannot be considered a reliable direct marker of sympathetic activity in long-term ambulatory ECG recording.
Key words: HRV, beta blockade, circadian patterns, sympathetic activity, autoregressive modeling, FFT.

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In a recently published study, our group has investigated the role of the spectral method and use of normalized spectral units for the assessment of heart rate variability (HRV) in the context of passive tilt test (1). Results from this study clearly indicated how autoregressive (AR) and Fast Fourier transform (FFT) spectral methods could lead to numerically different results associated with the mode of spectrum integration specific of each approach.

The role of spectral methodology for the quantification of circadian long-term sympathovagal changes and pharmacological autonomic manipulation on long-term electrocardiogram (ECG) is as controversial as with short-term HRV evaluation. Indeed, recent literature still presents conflicting results and a critical dilemma is the clinical implication of the use of normalized units.

Long-term spectral analysis has been applied in many clinical settings including normal patients (2,3,4,5), patients with coronary artery disease (6,7), congestive heart failure (8,9,10), postinfarction (11,12), and hypertension (13). With respect to circadian changes in normal patients, literature is concordant to detect a nocturnal increase of high frequency power (HF) regardless of the method used (2,4,6,11,13). On the contrary, day-night behavior of low frequency power (LF) is more debated with certain investigators claiming a nocturnal increase (4,5,6,9,12) while others state a decrease (2,7,11,14).

A complete understanding of the effect of sympathetic blockade on LF circadian rhythmicity seems to be characterized by similar questions. Cook et al. (3) showed an increase of LF raw power in normal volunteers after the administration of atenolol using an approach based on FFT; conversely, using an AR approach, Pagani et al. (15) found a significant decrease of normalized LF power after chronic beta-blockade (propranolol) and under controlled respiration. Other studies on pathological populations using both raw and normalized units claimed that LF power was either unchanged (12) or slightly increased (6,9).

Although spectral approach and, in particular, use of normalized units are often addressed to be the main sources of disagreement (16,17,18), a study comparing the 2 methods on the same population has never been published. Our objective was, thus, to apply both AR and FFT spectral analysis on 24-hour ambulatory ECG recordings and to compare raw and normalized LF and HF powers obtained with the 2 methods. The clinical implications are assessed with respect to circadian sympathovagal changes, both at baseline and after sympathetic blockade.

Materials and Methods

Study Population

Study population was part of a controlled trial designed to compare 2 parallel groups of mild hypertensive patients randomized either with bisoprolol (10 mg/d) or enalapril (20 mg/d), both administered once a day. Inclusion criteria were (1) patients in sinus rhythm of both sexes presenting with chronic uncomplicated mild hypertension (diastolic blood pressure between 95 and 115 mmHg) and (2) age under 70 years. Major noninclusion criteria were documented coronary artery disease, heart failure, diabetes mellitus, renal failure, and concomitant therapy known to affect the autonomic nervous activity.

After discontinuation of previous treatments, all study patients underwent ambulatory 24-hour Holter recording and 2-dimensional echocardiography at the time of enrollment and after 3 months of chronic administration of treatment. The protocol was approved by the ethical committee for biomedical research, Lyon, France, and written informed consent was obtained from all patients.

Forty-eight patients (33 men) were included in the trial, 25 in the bisoprolol group and 23 in the enalapril group. Four patients were discarded (2 in each treatment group) either for noncardiac adverse effects or technical problems with Holter recording. Tapes were considered eligible if they had at least 23 hours of analyzable data. For the purpose of the study, we retained the 44 baseline Holter observations and the 23 patients who underwent 2 recordings, 1 at baseline and 1 after chronic beta-blockade therapy.

Mean age of the global population (n = 44, 30 men) was 51 $\pm$ 12 years whereas that of the bisoprolol subgroup (n = 23, 15 men) was 50 $\pm$ 13 years. Mean shortening fraction by echocardiogram at the time of enrollment was 35% $\pm$ 8%.

Data Acquisition

Holter recordings were acquired with a dual-lead analog Holter recorder (ELA2448, ElaMedical, Le-Plessis Robinson, France). Patients were instructed to behave in a normal manner and to fill a diary form keeping track of usual daily physical activity. Analog data was digitized at 200 Hz (Elatec Holter system, ElaMedical) and edited by a cardiologist. The validation procedure consisted of beat labeling and tagging of noisy regions. Both ECG raw data and annotation information were transferred to a

personal computer for dedicated analysis. ECG digital files were first analyzed by an algorithm that (re)positioned the fiducial location of each sinus QRS complex after application of parabolic interpolation (19). Correction for nonsinus beats was performed with cubic spline interpolation. The continuous series of RR intervals (tachogram) was then obtained and all 5-minute segments with at most 5 isolated ectopic beats were retained for spectral analysis. Power spectral density (PSD) with both AR and FFT approaches was applied on the original (nonresampled) tachogram and was performed with research software developed in our institution.

Definition of Circadian Periods

Three circadian periods were considered, the complete 24 hours, the diurnal, and the nocturnal periods, defined on the basis of patient diaries. Diurnal periods covered lengths of at least 6 hours to a maximum of 10 hours; nocturnal periods covered a minimum of 4 hours to a maximum of 6 hours.

Time Domain Parameters

Classical time domain parameters were calculated over the 3 circadian periods considered. They were the average RR interval (ms), its SDRR (ms), PNN50 (%) and rMSSD (ms). Definition of these parameters can be found in the ESC/NASPE Task force document (20).

Spectral Analysis

FFT power spectrum was calculated with the method of averaged Periodogram (21,22). The tachogram to be analyzed was first divided in a number of overlapping subsegments. After windowing and mean value subtraction, a Periodogram for each of these subsegments was calculated. At the end of the procedure, the n Periodograms were averaged. The size of each subsegment was fixed to 128; then, n was the number of 128 RR sequences (50% overlapped) that could fit in the selected 5-minute period and varied between 3 and 6 (during the day) and between 3 and 5 (during the night). Windowing was achieved with a standard Hanning window, which included a correcting coefficient to account for loss of variance (23,24). Power within specific bands was calculated by integration (area under PSD curve) obtained with a trapezoidal rule.

Estimation of PSD with AR modelization is tightly linked with the identification of the model parameters (25,26). In this study, the parameters were identified with Levinson-Durbin algorithm (27) whereas Akaike criterion was used for the choice of model order (28). Linear detrending was performed before AR modelization. Frequency ranges were as follows (21): very low frequency (VLF): <0.04 Hz, LF: 0.04 to 0.15 Hz, HF: 0.15 to 0.4 Hz.

Each spectral estimate is based on a 5-minute segment. Then a potential sequence of 288 power spectra was obtained. Actually, a fraction of 5-minute segments was discarded for either noise or frequent ectopic beats (see earlier). With the AR method, a further excluding criterion is the possibility of not being able to fit an AR model. Besides, a successful AR modelization does not necessarily guarantee the presence of all spectral components, the presence of a component being associated with a well-defined oscillatory pattern with a precise central frequency. Thus, with the AR method, not only the total number of 5-minute sequences, but also that of VLF, LF, and HF available estimates could be less than that used with FFT.

Frequency Domain Parameters

The output data of a 24-hour recording consisted of a long sequence of parameters, 1 line for each 5-minute sequence. An extract from one of these outputs obtained with AR spectral analysis is displayed in Table 1. In the table the results of 6 consecutive spectra taken between 11.35 and 12.05 are reported. An asterisk indicates a missing value. For instance, in the spectrum estimated between 11.40 and 11.45 there were neither LF nor HF components. In the spectrum between 12.00 and 12.05 there was not an LF component. In both examples, the ratio between LF and HF components (LF/HF) was then also considered missing.

Diurnal, nocturnal, and 24-hour variables were calculated as the mean values of available 5-minute estimates of the respective parameter within the period considered. For instance, LF24h was the mean of all the values in the LF column of data output, excluding the lines for which LF was missing. LFDay was the mean of the nonmissing values of the same column corresponding to the lines belonging to the day. Owing to its strongly asymmetrical nature, LF/HF circadian parameters were not calculated as means but instead as medians.

Table 1. Extract of AR HRV Output

Hour	TP	VLF	LF	HF	LFnu	HFnu	VLFcf	LFcf	HFcf	LF/HF
11:35	1797	1592	104	69	51	34	0.000	0.097	0.278	1.50
11:40	3099	3033	*	*	*	*	0.000	*	*	*
11:45	240	178	28	21	45	34	0.018	0.110	0.396	1.33
11:50	1107	860	164	65	66	26	0.000	0.113	0.326	2.51
11:55	848	614	152	60	65	26	0.000	0.118	0.291	2.55
12:00	1814	1735	*	69	*	87	0.000	*	0.285	*

Thirty-minute extract from long-term spectral analysis with autoregressive modelization. Each line represents a single spectral estimation over a 5-minute segment. * Indicates a missing value for the corresponding parameter.

Statistical Analysis

Normalized LF and HF components were defined dividing the corresponding raw power by total power (TP) minus the power in the VLF band: LFnu = LF/(TP-VLF), HFnu = HF/(TP-VLF). All raw powers (TP, VLF, LF, and HF), log-transformed raw powers (lnTP, lnVLF, lnLF, and lnHF), normalized powers (LFnu, HFnu), and LF/HF ratio (which is independent of normalization) obtained with FFT and AR approaches were compared. Central frequencies of VLF, LF, and HF components (VLFcf, LFcf, HFcf, only available with AR) were also compared between baseline and treatment. Both FFT versus AR and (within the same approach) baseline versus beta-blockade comparisons were achieved with paired Wilcoxon signed-ranks test. Overall day versus night and baseline versus treatment changes in spectral powers obtained by both methods were compared using Bonferroni correction for multiple comparisons. A value of $P < .05$ was considered significant.

Results

Effects of Spectral Method On Circadian HRV Patterns

Table 2 summarizes the overall results of the 44 off-therapy recordings. Circadian patterns of time domain parameters show a significant nocturnal increase of RR, PNN50, and rMSSD whereas SDRR is comparable between the 2 periods. Behavior of spectral parameters depends on the use of normalized units. All raw power parameters, including the LF component, increase significantly at night, inde-

Table 2. Circadian Patterns of HRV in Baseline Recordings

	24 Hours		Day		Night	
RR (ms)	762 ± 86		695 ± 82		915 ± 123*	
SDRR (ms)	129 ± 38		78 ± 27		85 ± 32	
PNN50 (%)	6.9 ± 9.5		4.0 ± 7.6		14.1 ± 16.4*	
RMSSD (ms)	31 ± 17		24 ± 14		42 ± 28*	
	AR	FFT	AR	FFT	AR	FFT
TP (ms^2)	3028 ± 2734	2699 ± 2602†	2050 ± 2322	1688 ± 2001†	4680 ± 4275*	4465 ± 4283*†
lnTP	7.74 ± 0.74	7.57 ± 0.76†	7.28 ± 0.76	7.07 ± 0.81†	8.08 ± 0.88*	8.01 ± 0.89*†
VLF (ms^2)	2213 ± 1946	1359 ± 1352†	1503 ± 1638	756 ± 911†	3463 ± 3056*	2387 ± 2290*†
ln VLF	7.42 ± 0.71	6.89 ± 0.78†	6.96 ± 0.81	6.38 ± 0.88†	7.78 ± 0.85*	7.39 ± 0.89*†
LF (ms^2)	673 ± 633	798 ± 718†	495 ± 509	593 ± 618†	958 ± 1233*	1163 ± 1240*†
ln LF	6.13 ± 0.92	6.36 ± 0.81†	5.78 ± 0.94	6.01 ± 0.85†	6.28 ± 1.11*	6.6 ± 0.97*†
HF (ms^2)	390 ± 541	414 ± 550†	207 ± 422	227 ± 406†	666 ± 896*	715 ± 954*†
ln HF	5.34 ± 1.08	5.41 ± 1.04†	4.58 ± 1.04	4.79 ± 0.99†	5.8 ± 1.2*	5.9 ± 1.17*†
LFnu	57 ± 12	62 ± 9†	62 ± 15	65 ± 11†	49 ± 14*	56 ± 13*†
HFnu	36 ± 11	24 ± 8†	28 ± 11	19 ± 7†	46 ± 14*	33 ± 13*†
LF/HF	2.8 ± 1.9	3.4 ± 1.7†	4.5 ± 3.4	4.3 ± 1.9†	1.6 ± 1.2*	2.5 ± 1.8*†

Circadian patterns of time and frequency domain HRV parameters in baseline recordings. Spectral parameters are given independently for AR and FFT methods. Data shown are mean ± SD.

* $P < .01$ with respect to day.

† $P < .01$ with respect to AR method.

pendently of the mode of spectral computation (AR or FFT). Conversely, normalized powers have opposed circadian behaviors with decreasing LFnu (again with both spectral methods) and increasing HFnu. Figure 1 is a representative case in which the typical reversal of LF circadian trend when normalized units are used is shown.

Significant differences between AR and FFT are in the same direction for all circadian periods. Specifically, total powers and VLF powers are systematically significantly larger with AR estimation. On the contrary, LF and LFnu are larger with the FFT method. Raw HF powers are larger with FFT whereas HFnu are larger with AR. Finally, the LF/HF ratio tends to be larger with FFT but not for the diurnal period. Overall day versus night analysis (not in Table) confirmed a significant increase of all raw powers and HFnu and a decrease of LFnu and LF/HF.

Central frequencies (only available with AR, not shown in Table) also present a circadian pattern: VLFcf is increased from a pure 0 Hz component during the day to a 0.007 Hz mean value at night whereas LFcf and HFcf decreased significantly at night (respectively from 0.09 and 0.27 Hz to 0.08 and 0.25 Hz, $P < .05$).

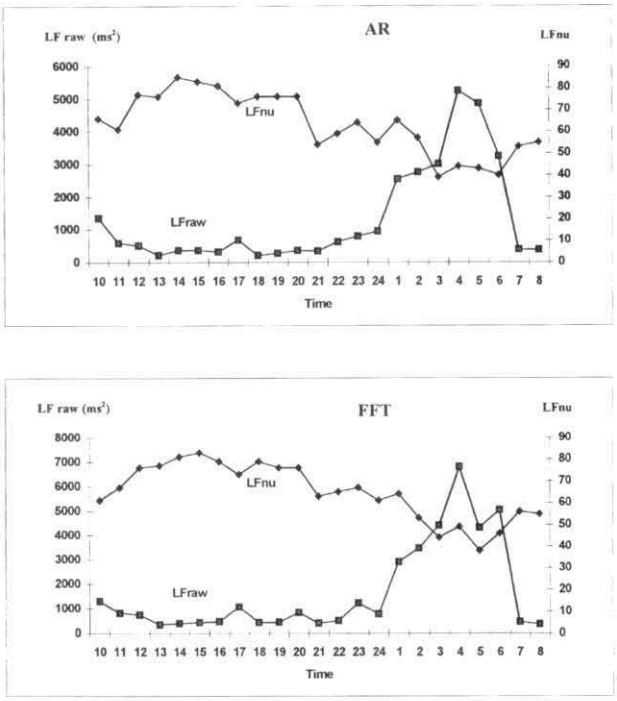

Fig. 1. Hourly trends of raw and normalized LF components with AR (top) and FFT (bottom) spectral methods in a baseline patient. With both spectral methods, the nocturnal behavior of raw LF shows a clear augmentation whereas that of LFnu indicates a decrease.

Effects of Spectral Method on Sympathetic Blockade Assessment

Table 3 shows the effect of bisoprolol administration on time- and frequency-domain HRV parameters for the 23 patients randomized to beta-blocker treatment. In particular, baseline results are consistent with those of the complete population presented in Table 2. Numerical differences between AR and FFT outputs under beta-blocker are in the same direction of those observed in basal condition.

All time-domain parameters (except SDRR of 24 hour) were increased significantly under beta-blockade. This effect was also observed in the frequency domain for raw powers and with both spectral methods used. Some of the raw power increases failed to reach statistical significance (eg, LF by FFT at night), probably owing to large intravariations. In fact, the log-transformed raw powers were systematically increased with $P < .01$.

Table 4 shows the variation of all spectral parameters (bisoprolol-baseline). The magnitude of HF component increase is close to that of LF increase; however, the HF increase induced by the beta-blocker is proportionally more important because it starts from a smaller basal value (Table 3). This effect is clearly magnified by normalized units. Indeed, normalization procedure strongly affects the variations associated with beta-blockade, the HF increase being further amplified (eg, with AR, diurnal HFnu is increased from 26 ± 11 to 39 ± 14, $P < .01$) whereas that of raw LF power being annulled (eg, with AR, diurnal LFnu goes from 62 ± 18 to 59 ± 11, not significant). Tendency of LF/HF ratio after beta-blockade is to decrease, though statistical significance is only reached with AR method at day and with FFT at night.

Circadian patterns of raw powers under sympathetic blockade confirm those at baseline, ie, an increased nocturnal variability. More specifically, the reversed pattern of LF raw power and LFnu is maintained. Figure 2 shows hourly raw and LFnu powers for a specific case at baseline and after beta-blockade. The nocturnal decrease of LFnu after beta-blockade remains apparent. In addition, whereas raw LF tends to be larger after beta-blockade the behavior of LFnu is more erratic. Finally, overall treatment versus baseline analysis confirmed an increase of all spectral powers with the exception of an unchanged LFnu.

Table 3. Effect of Beta-Blockage on HRV

	24 Hours				Day				Night			
	Baseline		BB		Baseline		BB		Baseline		BB	
RR	761 ± 82		923 ± 131*		690 ± 77		877 ± 136*		922 ± 123†		1061 ± 152*†	
SDRR	132 ± 42		138 ± 41		74 ± 23		99 ± 33*		85 ± 34		102 ± 34*	
PNN50	7.2 ± 9.7		13.8 ± 12.2*		3.8 ± 7.4		10.7 ± 12.3*		15.0 ± 17.1†		24.1 ± 19.0*†	
Rmssd	33 ± 18		44 ± 25*		24 ± 14		38 ± 23*		45 ± 29†		58 ± 39*†	
	AR	FFT	AR	FFT	AR	FFT	AR	FFT	AR	FFT	AR	FFT
TP(ms^2)	3006 ± 2853	2697 ± 2794	4484 ± 3323*	4069 ± 3082*	2000 ± 2319	1643 ± 1982	3668 ± 2319*	3212 ± 3340*	4600 ± 4113†	4411 ± 4301†	6348 ± 4297†‡	6117 ± 4117†‡
ln TP	7.72 ± 0.74	7.58 ± 0.78	8.15 ± 0.71*	8.06 ± 0.76*	7.25 ± 0.83	7.02 ± 0.83	7.83 ± 0.88*	7.65 ± 0.92*	8.11 ± 0.81†	8.06 ± 0.85†	8.52 ± 0.78†*	8.45 ± 0.81*†
VLF(ms^2)	2139 ± 2003	1306 ± 1451	3284 ± 2323*	2090 ± 1618*	1411 ± 1542	688 ± 837	2679 ± 2502*	1564 ± 1654*	3383 ± 3082†	2305 ± 2405†	4802 ± 3105†*	3239 ± 2215*†
ln VLF	7.39 ± 0.71	6.86 ± 0.74	7.9 ± 0.64*	7.42 ± 0.69*	6.9 ± 0.85	6.15 ± 0.88	7.55 ± 0.83*	6.96 ± 0.9*	7.81 ± 0.81†	7.39 ± 0.83†	8.24 ± 0.74†*	7.85 ± 0.76*†
LF(ms^2)	700 ± 688	816 ± 793	932 ± 736‡	1077 ± 831*	534 ± 550	612 ± 650	873 ± 921‡	993 ± 1024*	928 ± 1030§	1133 ± 1162†	1133 ± 949‡	1334 ± 934
ln LF	6.08 ± 1.01	6.33 ± 0.85	6.47 ± 0.92*	6.7 ± 0.78*	5.76 ± 1.13	5.99 ± 0.97	6.47 ± 0.92*	6.45 ± 0.97*	6.29 ± 1.08§	6.6 ± 0.92†	6.6 ± 1.04*	6.9 ± 0.83*†
HF(ms^2)	414 ± 521	425 ± 536	677 ± 671‡	727 ± 753‡	194 ± 410	221 ± 396	429 ± 550*	491 ± 619*	699 ± 834†	757 ± 911†	1220 ± 1320†‡	1321 ± 1484†‡
ln HF	5.39 ± 1.15	5.44 ± 1.11	5.99 ± 1.13*	6.03 ± 1.15*	4.54 ± 1.01	4.74 ± 1.04	5.32 ± 1.27*	5.48 ± 1.24*	5.6 ± 1.24†	5.96 ± 1.24†	6.49 ± 1.22†*	6.59 ± 1.22*†
Lfnu	57 ± 13	61 ± 10	54 ± 10	60 ± 9	62 ± 18	65 ± 14	59 ± 11	64 ± 9	47 ± 16†	55 ± 14§	46 ± 13†	52 ± 13†
Hfnu	36 ± 11	24 ± 8	45 ± 11*	30 ± 9‡	26 ± 11	18 ± 6	39 ± 14*	24 ± 8‡	48 ± 16†	34 ± 14†	54 ± 12†‡	41 ± 13*†
LF/HF	2.7 ± 1.5	3.4 ± 1.2	2.1 ± 1.2	2.8 ± 1.1	4.8 ± 3.5	4.4 ± 1.9	3.1 ± 2.4‡	3.4 ± 1.4	1.7 ± 1.5†	2.3 ± 1.7†	1.2 ± 0.9†	1.7 ± 1.1†‡

Effects of bisoprolol administration on time and frequency domain HRV parameters. Spectral parameters are given independently for AR and FFT methods. Data shown are mean ± SD
* $P < .01$ with respect to baseline.
† $P < .01$ with respect to day.
‡ $P < .05$ with respect to baseline.
§ $P < .05$ with respect to day.

Table 4. Delta Values of HRV Parameters After Beta-Blockade

	24 Hours		Day		Night	
	AR	FFT	AR	FFT	AR	FFT
ΔTP (ms^2)	1478 ± 1977*	1309 ± 1889*	1668 ± 1998*	1399 ± 1821*	1749 ± 3082†	1979 ± 3089†
ΔlnTP	0.44 ± 0.39*	0.46 ± 0.44*	0.58 ± 0.48*	0.62 ± 0.48*	0.39 ± 0.44*	0.41 ± 0.46*
ΔVLF (ms^2)	1145 ± 1296*	709 ± 1377*	1269 ± 1456*	808 ± 1011*	1418 ± 2182*	1042 ± 1551*
ΔlnVLF	0.48 ± 0.41*	0.55 ± 0.44*	0.64 ± 0.48*	0.81 ± 0.58*	0.44 ± 0.51*	0.44 ± 0.48*
ΔLF (ms^2)	232 ± 410†	216 ± 534*	339 ± 594†	335 ± 485*	206 ± 475†	287 ± 611
ΔlnLF	0.39 ± 0.53*	0.35 ± 0.44*	0.48 ± 0.78*	0.46 ± 0.55*	0.35 ± 0.51*	0.3 ± 0.48*
ΔHF (ms^2)	263 ± 575†	312 ± 677†	234 ± 370*	225 ± 427*	521 ± 1163†	617 ± 1284†
ΔlnHF	0.6 ± 0.78*	0.6 ± 0.81*	0.78 ± 1.06*	0.74 ± 0.99*	0.6 ± 0.81*	0.62 ± 0.78*
ΔLFnu	−3.4 ± 12	−1.04 ± 13	−3.6 ± 16	−2.3 ± 11	−2.0 ± 12	−2.3 ± 11
ΔHfnu	9.1 ± 12*	5.0 ± 11†	12.6 ± 16*	5.5 ± 11†	7.5 ± 13†	6.9 ± 11*
ΔLF/HF	−0.6 ± 1.5	−0.13 ± 4.5	−1.7 ± 3.2†	−0.9 ± 2.4	−0.5 ± 1.5	−0.6 ± 1.4†

Variations of spectral HRV parameters after beta-blockade.
Data shown are mean ± SD of differences between BB and Baseline; * $P < .01$; † $P < .05$.

Discussion

To our knowledge, this is the first study in which FFT and AR methods were applied on the same population to evaluate circadian sympathovagal changes and the effect of sympathetic blockade from long-term ECG recordings. The major findings can be summarized as follows:

1. qualitative assessment of circadian patterns and beta-blockade effect on HRV do not depend on spectral methodology;
2. circadian pattern of LF component depends on use of normalized units, thus, implications on the physiological origin of the LF component from long-term ECG recording is not affected by the spectral method but only by the normalization procedure;
3. the lack of a significant decrease in LFnu after beta-blockade indicates that this parameter cannot be considered as a reliable direct marker of sympathetic activity in long-term ambulatory ECG recording.

Power spectral analysis of heart rate variability has been claimed to provide a window in which the sympathetic and parasympathetic neural influences to sinus node firing can be evaluated (29,30). It is suggested that the HF component represents vagal activity and the LF component sympathetic modulation, whereas LF/HF ratio is associated to sympathovagal balance (17); However, the physiological origin of the LF component is still debated. Many studies have used long-term ambulatory recordings forgetting that LF and HF components depend on breathing rate (31,32), physical activity (33), baroreceptor function (34), food intake (35), and even on the sequence of excitation, vagal or sympathetic activity being first (36).

Spectral Method in the Context of Ambulatory Uncontrolled Long-term ECG Recordings

Although many spectral methods have been applied, the 2 by large most popular are autoregressive and FFT-based approaches. As clearly shown in both Tables 2 and 3, these 2 methods give numerically different results. To our knowledge, the 2 methods were previously only compared either in

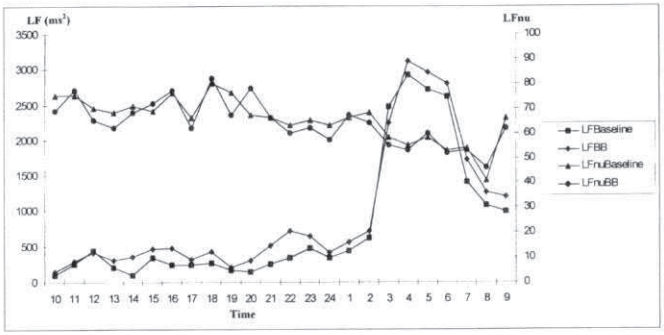

Fig. 2. Hourly trends of raw and normalized LF components before and after beta-blockade administration for a representative patient. The increased LF power after beta-blockade is apparent (LFBaseline and LFBB curves). Conversely, normalized LF power is unchanged after beta-blockade (LFnuBaseline and LfnuBB curves).

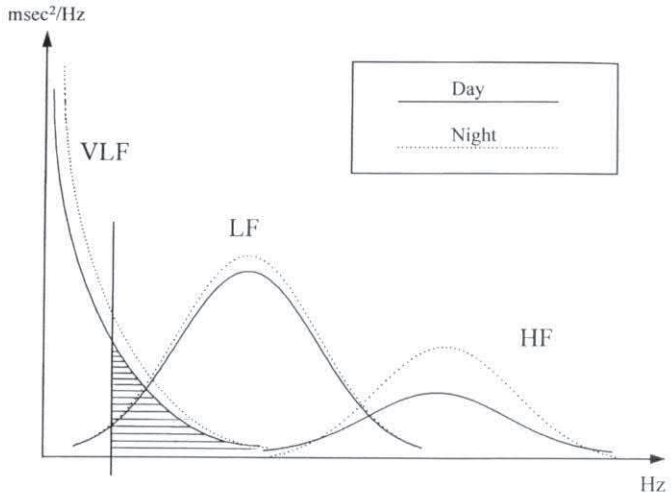

Fig. 3. Schematic representation of tailing effect and of nocturnal changes of power spectral density. Vertical line marks the cut off between VLF and LF bands. The solid line area shown the diurnal VLF tail power that is assigned to LF band with FFT method, thus, resulting in a larger LF power and a smaller VLF power. At night, all spectral components are augmented but the proportional increase of HF is more important than that of LF, thus, resulting in a decreased normalized LF. Despite its more important increase, magnitude of nocturnal HF raw powers remains smaller than that of LF.

the context of tilt test (1) or during self-management therapy (37). Whereas in the first study quantitative differences were found, the latter report, only based on 5 patients, simply concluded that results from the 2 approaches were highly correlated, though AR showed better resolution of sharp peaks. In this section, the possible sources of discrepancies with specific emphasis on the particular conditions of ambulatory ECG recordings are discussed.

Differences observed in total powers are probably related to the permanently changing environment providing strong heart rate trends (physical activities, sleep states). These differences are likely owing to the specific preprocessing of Average Periodogram associated with FFT, where the initial sequence is divided in multiple shorter overlapping sequences, each of them independently detrended by mean subtraction (21). In a previous article, we have shown that under the strictly controlled conditions of tilt test, the preprocessing effects are negligible because only very stable tachograms are present with a trend slope close to 0 and total powers of the 2 methods were identical (1). Conversely, in the completely uncontrolled environment of ambulatory recordings, significant data trends are frequent and the more aggressive trend removal of FFT thus explains the smaller total powers observed with the FFT method.

Other differences between AR and FFT are tightly linked to the procedure used for power integration within a band by the 2 approaches. With FFT, the power within a band is the integral (area under the curve) calculated from lower to upper band limit whereas with AR it is the effective power associated with a spectral component with central frequency inside the band (38). This feature of spectral power computation can lead to numerical differences, particularly when 2 neighboring components are different in magnitude. In such cases, the big tail of the larger component invades the band of the neighbor component and the corresponding power will be assigned to the other band by the FFT method (1), as shown in Figure 3. In ambulatory recordings, PSD is characterized by a large VLF, followed up by smaller LF and by an even smaller HF. We are thus in the presence of 2 tail effects, 1 between VLF and LF that explains the larger LF power of FFT, the other between LF and HF, which explains the larger HF power of FFT.

Despite these differences, it is remarkable to observe how dynamical trends are consistent with both methods. For example, by looking at Table 2 we can fairly state that, regardless of the spectral method: (1) raw HF and HFnu increase at night, (2) raw LF increases at night, and (3) LFnu and LF/HF decrease at night. Thus, the qualitative assessment over 24 hours of autonomic changes is not jeopardized by the spectral method.

Circadian HRV Patterns at Baseline

As shown in Table 2, we confirm a parallel nocturnal increase of all raw powers as already observed by many studies (4,39). Of course, the residual power used as the divisor for the calculation of LFnu and HFnu (TP-VLF) is also augmented. After normalization, the LF and HF powers do not behave in the same way, nocturnal LFnu is diminished whereas nocturnal HFnu is still increased.

Figure 1 highlights the divergent circadian behaviors of raw LF and LFnu. Figure 3 helps to understand why only LF trends are affected by the

normalization whereas HF trends do not. Both components increase at night but proportionally HF variations are larger (with AR, 4-fold HF vs 2-fold LF increases, Table 2). Thus, the magnitude of the nocturnal HF increase is able to counterbalance the parallel increase of residual power whereas that of LF is overthrown. This is also enhanced by the LF/HF ratio, which shows a strongly significant nocturnal decrease.

Our study clearly shows how this particular behavior is common to both spectral methods and not a privilege of AR approach. Therefore, it might well be the case that the debate about the discrepancies between the 2 methods regarding circadian trends is a consequence of the lack of a comparative study, FFT-based reports generally ignore normalization (3,4) whereas AR-based studies are associated with normalization (2,11).

Another finding is the presence of circadian modulation in both LF and HF central frequencies, which are significantly shifted from day to night (from 0.09 and 0.27 Hz to 0.08 and 0.25 Hz, respectively). In other words, the periods (in seconds) of autonomically mediated RR oscillations are longer at night. These results are in agreement with those of Lombardi et al. (11) and Furlan et al. (2) on similar populations and with the same spectral method. At present, the clinical implications of these moderate changes are unknown.

Effect of Bisoprolol on HRV

After chronic administration of bisoprolol, time domain parameters are significantly increased, thus, confirming the adequacy of beta-blockade (Table 3). All spectral raw powers are increased significantly (only LF has a statistically weaker increase). Again, the use of normalization procedure has drastic consequences: the increase in HF is magnified whereas that of LF loses its statistical significance. Thus, the main consistent effect of bisoprolol administration seems to be the increase of HF power. Once again, in spite of different values, the information gained does not depend on the spectral method.

Most studies investigating the effects of beta-blockers on HRV used the FFT approach. In normal patients, Cook et al. (3) reported an increased HF power after drug intake (atenolol, 200 mg/d) with moderate changes in the LF component. Similar results where obtained in post-MI patients after administration of metoprolol (12). In the CIBIS trial, the relative increase of HF component after intake of bisoprolol was the more important (9). Finally, Burger and Kamalesh (6) analyzed HRV parameters in patients with coronary artery disease before and after administration of either atenolol or betaxolol; raw HF power was increased and raw LF power was unchanged. The only study assessing the effect of beta-blockade with an AR approach is the pioneer work of Pagani et al. (15). Curiously enough, this is also the only study in which normalized units (but not raw powers) were used. Unfortunately, this study was conducted under very controlled conditions with short-term ECG recordings, and for this reason it cannot be strictly compared with those applied on ambulatory data. LF normalized units were significantly reduced by about 20% whereas HFnu were augmented by about 30%.

Although confirming the results of literature, results from this article allow the authors to add that the more evident HF increase after sympathetic blockade is also confirmed by AR approach. Use of normalized units eventually indicates a small decrease of LF, but is too weak to reach statistical significance. We should conclude that the logical circadian pattern of LF normalized component does not make it an acceptable direct surrogate of the sympathetic activity, at least in ambulatory long-term monitoring in which almost major modulators of the autonomic nervous system cannot be strictly controlled or simply recorded. Thus, implications on the physiological origin of noninvasive markers such as heart rate variability parameters should be confined in the context of highly specific dynamic tests (40–45).

Finally, it should be remembered how our findings are obtained from mild hypertensive patients and cannot be extrapolated to situations with shown autonomic impairment, such as heart failure (32), and postinfarction patients (46), in which the clinical role of LF component could be more clear.

Conclusions

Autoregressive- and FFT-based spectral approaches in long-term ambulatory ECG recordings provide numerically different results that can be explained by both differences in the preprocessing and in the procedure used for power integration within a band used by the 2 approaches. However, circadian heart rate variability patterns and beta-blockade effects are equally assessed by the 2 methods. Consideration of normalization procedure has a strong impact on long-term heart rate variability parameters, regardless of spectral method. Precisely, use of

normalized units for the evaluation of circadian changes makes the behavior of LF and HF in opposition. On the other hand, spectral analysis of heart rate variability is not capable of accounting for blockade of adrenergic receptors except for a an augmentation of parasympathetic activity. The original desire was that spectral analysis, in opposition to time domain, would have permitted an independent and separate picture of sympathetic and vagal activities; as of today, this hope has not yet been fulfilled with ambulatory Holter recordings.

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