Power Spectrum Analysis of Heart Rate Variability to Assess the Changes in Sympathovagal Balance During Graded Orthostatic Tilt

Nicola Montano, MD; Tomaso Gnocchi Ruscone, MD; Alberto Porta, BS; Federico Lombardi, MD; Massimo Pagani, MD; Alberto Malliani, MD

Background The powers of the low-frequency (LF) and high-frequency (HF) oscillations characterizing heart rate variability (HRV) appear to reflect, in their reciprocal relationship, changes in the state of the sympathovagal balance occurring during numerous physiological and pathophysiological conditions. However, no adequate information is available on the quantitative resolution of this methodology.

Methods and Results We studied 22 healthy volunteers (median age, 46.5 years) who were subjected after a rest period to a series of passive head-up tilt steps randomly chosen from the following angles: 15°, 30°, 45°, 60°, and 90°. From the continuous ECG, after appropriate analog-to-digital conversion, a personal computer was used to compute, with an autoregressive methodology, time and frequency domain indexes of RR interval variability. Spectral and cross-spectral analysis with the simultaneously recorded respiratory signal excluded its contribution to LF. Age was significantly correlated to variance and to the absolute values in millisecond squared of very-low-frequency (VLF), LF, and HF components. The tilt angle was correlated to both LF and HF (expressed in normalized units [nu]) and to the LF-to-HF ratio (r=.78, -.72, and .68, respectively). Lower levels of correlation were found with HF (in ms²) and RR interval. No correlation was present between tilt angle and variance, VLF, or LF (in ms²). Individual analysis confirmed that the use of nu provided the greatest consistency of results.

Conclusions Spectral analysis of HRV, using nu or LF-to-HF ratio, appears to be capable of providing a noninvasive quantitative evaluation of graded changes in the state of the sympathovagal balance. (Circulation. 1994;90:1826-1831.)

Key Words • tilt • sympathetic excitation • vagal withdrawal

During the past 13 years, the provocative hypothesis by Akselrod et al.1 that “quantitative analysis of fluctuations in hemodynamic parameters is a powerful quantitative means of probing mechanisms of short-term cardiovascular control” has opened a new field of impetuous research. The components of cardiovascular control taken into consideration by these authors were the sympathetic and parasympathetic efferent activities and the renin-angiotensin system, the respective roles of which were mainly explored with selective pharmacological blockade. Since our initial studies,2,3 we have proposed to couple the analysis of heart rate variability (HRV) to the concept of sympathovagal balance. This assumes that the interplay between sympathetic and vagal modulations of sinus node pacemaker activity is organized in a reciprocal fashion, i.e., that increased activity in one system is accompanied by decreased activity in the other. In addition to its biological likelihood, this general concept appears to be supported by precise experimental findings such as the opposite reflex responses to the same stimuli characterizing single nerve fibers, sympathetic or vagal, isolated from the same cardiac nerve.4 In this approach, the two neural outflows are considered together, in their natural interaction, without artificial separations.5

We have recently summarized6,7 the evidence indicating that in the spectral analysis of HRV, the powers of the low-frequency (LF) and the high-frequency (HF) components, occurring in synchrony with vasomotor waves3,4 and respiratory acts, respectively, appear to reflect in their reciprocal relationship the state of the sympathovagal balance in numerous physiological and pathophysiological conditions. However, adequate information regarding the quantitative resolution of the whole methodology is not yet available.

We report that power spectrum analysis of HRV can noninvasively quantify the changes in sympathovagal balance accompanying graded passive tilt.

Methods

Study Population

The study population included 22 healthy, nonsmoking volunteers of either sex (median age, 46.5 years; range, 22 to 66 years). A detailed medical history and examination excluded the evidence of any organic disease. Informed consent was obtained from all subjects. The study has been approved by our institution’s review board.

Recorded Variables

For each subject we recorded on an FM instrumentation tape (Racal) the surface ECG (CMS) with a conventional AC
amplifier and respiratory activity with a nasal thermistor (Nihon Kohden).

All subjects were studied at about 3:00 PM after they consumed a very light lunch free of alcohol or caffeine beverages; they were studied in a quiet, dimly lit room at a comfortable temperature (22 to 24°C). They were loosely strapped to an electrically driven tilt table that had a foot rest. After a period of adaptation in the supine position, analog data acquisition was initiated for resting conditions. After 15 minutes of continuous recording, we rotated the table, which had an electric motor, to an upright position (head-up tilt) that was maintained for 10 minutes. The inclination of the table was varied, randomly set at the following angles: 15°, 30°, 45°, 60°, and 90°. After each step, the subjects were moved again to a horizontal position for 10 minutes. The entire procedure took approximately 105 minutes. None of the subjects experienced syncope or presyncopal symptoms during the recordings. Subjects were not allowed to sleep. To minimize subjects' emotional arousal, we did not collect blood samples.

**Data Analysis**

Data were analyzed off-line with a personal computer (486 SX/25 MHz, Compaq) after appropriate analog-to-digital conversion at a rate of 300 samples per second per channel, using a 12-bit converter (Data Translation). The principles of the software for data acquisition and spectral analysis have been described elsewhere. In brief, from the ECG signal a derivative/threshold algorithm provided the continuous series of RR intervals (tachogram). Stationary segments devoid of arrhythmias (200 to 500 RR intervals) were analyzed with autoregressive algorithms. Autoregressive algorithms can automatically furnish the number, center frequency, and associated power of oscillatory components, without the need for a priori decisions. They rely on a posteriori formal statistical criteria, such as Anderson’s test (which verifies that all information contained in the data series is extracted in the computation) or Akaike’s criterion (which indicates the optimal model order fitting the data). An additional potential advantage of the autoregressive approach relates to an efficient spectral estimation on short segments of data, which are more likely to be stationary.

Two major oscillatory components are usually detectable in RR variability (Figs 1 and 2), one of which, synchronous with respiration, is described as HF (about 0.25 Hz and varying with respiration), whereas the other, corresponding to the slow waves of arterial pressure, is described as LF (about 0.1 Hz). However, the center frequency of the LF component can vary considerably (from 0.04 to 0.13 Hz).

In addition, the component below 0.03 Hz and with a center frequency around 0 Hz contributes substantially to total power as it can represent 40% to 50% under resting conditions and as much as 80% to 85% during standard Holter recording. This component contains noise, slow trends, and possibly very slow oscillations; therefore, to be adequately analyzed, it requires longer series of data and different algorithms. However, there are peculiar circumstances, such as markedly periodic breathing, in which clear oscillatory components are also detectable with the usual spectral methodology in this frequency range. Therefore, this part of the spectrum can be defined as either a DC component or a term that emphasizes the contribution of the nonrhythmic variations, or as a very low-frequency (VLF) component, which alludes to the possibility that it might also contain some hidden rhythmicity.

The LF and HF oscillatory components are presented both in absolute (ms²) and in normalized units (nu) (Fig 1). The nu are obtained with the following relation:

\[
P[nu] = \frac{P[ms^2]}{\sigma^2[ms^2] - P_{VLF}[ms^2]} \times 100
\]
TABLE 1. Spearman Univariate Correlation Between Table Incline and Time and Frequency Domain Indexes of RR Interval Variability

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>−.44</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>−.08</td>
<td>NS</td>
</tr>
<tr>
<td>VLF, ms$^2$</td>
<td>−.18</td>
<td>NS</td>
</tr>
<tr>
<td>VLF, %</td>
<td>−.16</td>
<td>NS</td>
</tr>
<tr>
<td>LF, ms$^2$</td>
<td>.17</td>
<td>NS</td>
</tr>
<tr>
<td>LF, %</td>
<td>.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LF, nu</td>
<td>.78</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HF, ms$^2$</td>
<td>−.41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HF, %</td>
<td>−.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HF, nu</td>
<td>−.72</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LF-to-HF ratio</td>
<td>.68</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

VLF, very low frequency; LF, low frequency; nu, normalized units; and HF, high frequency. n=22.

where $P$ represents the power of either LF or HF components, in [nu] or [ms$^2$]; $\sigma^2$ represents total power (equivalent to variance computed with time domain approaches), and $P_{VLF}$ indicates the power of the VLF component.

In addition, the percentage values of LF and HF components in respect to total power are presented in Tables 1 and 2, evidence of the importance of subtracting the VLF component.

The signal of respiratory activity was sampled once for every cardiac cycle, in correspondence with the R wave, thus obtaining a respirogram synchronized with the tachogram. These two series were used for further cross-spectral analysis (Fig 2).

Statistical Analysis

Unless otherwise indicated, data are expressed as mean±SEM. Nonparametric Spearman’s correlation analysis was performed on the overall population with SIGMASTAT (Jandel Co); computation of Theil linear regressions and Kendall’s $\tau$ was performed on individual data using IMSL.

TABLE 2. Spearman Univariate Correlation Between Age and Time and Frequency Domain Indexes of RR Interval Variability Assessed Over a Range of Tilt Incline From 0° to 90°

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>.01</td>
<td>NS</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>−.58</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VLF, ms$^2$</td>
<td>−.29</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VLF, %</td>
<td>−.14</td>
<td>NS</td>
</tr>
<tr>
<td>LF, ms$^2$</td>
<td>−.60</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LF, %</td>
<td>−.01</td>
<td>NS</td>
</tr>
<tr>
<td>LF, nu</td>
<td>−.01</td>
<td>NS</td>
</tr>
<tr>
<td>HF, ms$^2$</td>
<td>−.41</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HF, %</td>
<td>−.08</td>
<td>NS</td>
</tr>
<tr>
<td>HF, nu</td>
<td>−.08</td>
<td>NS</td>
</tr>
<tr>
<td>LF-to-HF ratio</td>
<td>.006</td>
<td>NS</td>
</tr>
</tbody>
</table>

VLF indicates very low frequency; LF, low frequency; nu, normalized units; and HF, high frequency. n=22.

In all subjects, LF and HF components were present in the spectra of RR interval variability (Figs 1 and 2). The respiratory activity was significantly coupled only with the HF component of RR variability, as indicated by a high degree of coherence existing between these variability signals in correspondence with HF component. In the example of Fig 2 a 90° tilt incline was accompanied, as already reported,\textsuperscript{2,3,5,6,10,17} by an increase in LF and a decrease in HF component. In addition, a slight gradual increase in main respiratory frequency was associated with rising tilt incline (for the entire population from 0.23±0.01 to 0.28±0.01 Hz; $r=.$31, $P<.01$). A significant contribution of respiratory activity to LF component\textsuperscript{3,18} was excluded for all subjects during the entire protocol.

The degree of tilt incline was correlated to a gradual significant reduction of RR interval, whereas no significant correlation was observed in the case of RR variance or VLF component (Fig 3; Table 1). With regard to variance, the values at 90° were significantly ($P<.01$) smaller than those at 0°, as in a previous study.\textsuperscript{3}

As anticipated (see “Methods”), LF and HF components were evaluated in both absolute units and nu. When LF was expressed in absolute units, no significant correlation was present with tilt incline (Fig 3) and the values at 90° were not significantly different from those at 0°. Conversely, HF in absolute units was significantly correlated with the degree of tilt ($r=.$41, $P<.001$). However, a strong correlation was found between the degree of tilt incline and LF and HF components expressed in nu ($r=.$78 and $−.72$, $P<.001$, respectively) (Fig 3). A significant, although weaker, correlation was found between tilt incline and LF and HF components expressed as percent of total power (which includes the VLF component). Finally, a strong correlation was present with LF-to-HF ratio ($r=.$68, $P<.001$) (Fig 3). The uneven statistical links between tilt incline and various measures of RR variability are summarized in Table 1.

Since our initial studies,\textsuperscript{3} we have proposed the use of a normalization procedure to minimize the confounding effects of the large differences in variance that are found among subjects due to aging\textsuperscript{5,19} or various pathophysiological conditions.\textsuperscript{5} In the present study, age was significantly correlated with variance ($r=.$58) and with the absolute values of spectral components expressed in milliseconds squared (VLF, $r=.$29; LF, $r=.$60; HF, $r=.$41; $P<.001$ in all cases) (Table 2). Conversely, the normalized values of LF and HF components did not correlate with age (Table 2).

It should be added that a strong statistical link existed between variance and VLF ($r=.$64), LF ($r=.$84), and HF ($r=.$71) in milliseconds squared. No correlation was present between variance and spectral components expressed in percent (VLF, LF, HF) or nu (LF, HF). However, in view of their mathematical relation, a strong correlation ($r=.$91) was also present between LF and HF in nu.

Regarding individual analysis, the nonparametric Theil regressions for absolute and normalized values of
the indexes derived from RR interval variability as a function of the tilt angle allowed us to quantify their consistency and associated probability in sensing tilt incline.

As shown in Table 3, the use of nu furnished the greatest consistency of results as the regressions of LF against tilt angle were in all cases (100%) significant, and nearly so in the case of HF (91%; confidence limits, 73% to 99%). Regressions of the absolute power of spectral components, of LF-to-HF ratio, or of variance against tilt angle were less likely to be significant in this restricted population.
TABLE 3. Nonparametric Individual Theil Regressions Between Tilt Incline and Measures of RR Interval Variability

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percent Significant</th>
<th>Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>73 (54-89)</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>ω²</td>
<td>36 (18-59)</td>
<td>NS</td>
</tr>
<tr>
<td>VLF, ms²</td>
<td>18 (5-40)</td>
<td>NS</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>32 (15-55)</td>
<td>NS</td>
</tr>
<tr>
<td>LF, nu</td>
<td>100</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>59 (38-79)</td>
<td>NS</td>
</tr>
<tr>
<td>HF, nu</td>
<td>91 (78-99)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LF-to-HF ratio</td>
<td>64 (44-82)</td>
<td>NS</td>
</tr>
</tbody>
</table>

VLF indicates very low frequency; LF, low frequency; nu, normalized units; and HF, high frequency.

*Percent of individual regressions in the entire population (n=22) with a Kendall’s τ passing the significance level.

†Probability refers to the likelihood of occurrence of the observed data, considering a binomial distribution with the hypothesis of 50% significant and 50% nonsignificant regressions due to chance.

Discussion

This study demonstrates the capability of spectral analysis of HRV to quantify graded changes in sympathovagal balance induced by passive tilt. The current opinion is that the slight tachycardia usually accompanying upright posture is the result of a sympathetic excitation associated to a vagal withdrawal in the neural modulation of sinus node pacemaker activity.20 While the occurrence of a sympathetic excitation has been deduced from a number of indirect measurements, such as that of circulating catecholamine concentration,21 the occurrence of a vagal withdrawal is largely inferential.22 In fact, the widely accepted corollary concept of sympathovagal balance is supported by relatively few direct observations based on the reciprocal functional patterns characterizing the impulse activity of the two neural outflows directed to the heart.4,23

Within the extension of this general scheme, one could conceive the sympathetic excitation and vagal withdrawal characterizing the orthostatic position as the end point in a continuum of intermediate changes in parallel to the progression of the stimulus. Accordingly, we selected the use of passive tilt as the most appropriate stimulus to induce graded changes in sympathovagal balance, also in view of some further crucial advantages offered by this maneuver.

Passive tilt only entails a minimal engagement of central drive and muscular activity and is compatible with quite accurate stationary conditions, a prerequisite for the safest use of spectral methodology; this differs from physical exercise, which is progressively characterized by marked to extreme reductions in RR variability signal, by the presence of nonlinearities and nonstationarities, and by an enhanced respiratory activity.24-26

The results of this study indicate that the normalization procedure of spectral components provides an efficient use of power spectral analysis of HRV to assess the progression of a sympathetic excitation, of a concomitant vagal withdrawal, and, consequently, of a shift in sympathovagal balance. Accordingly, normalized values of both LF and HF components were characterized by the highest degree of correlation. On the other hand, the weaker correlation existing between degree of tilt and LF and HF components expressed as percent values of total power was likely to be due to the confounding effect of VLF, which is not subtracted in this type of computation.

With regard to variance, its decrease in correspondence with maximal inclination of tilt is important to interpret the concordant or discordant changes of the absolute or normalized values of HF and LF components. In the case of the absolute values of HF, despite their marked dispersion, they were capable of signaling the progression of the stimulus, and their gradual reduction was concordant with that of their normalized values. Conversely, in the case of the absolute values of LF, they underwent contrasting influences during tilt; they tended to be decreased by the reduction of variance, but they also tended to be increased by the greater concentration of residual power in the LF component, as reflected by its constant rise in nu. Therefore, the absolute values of LF were incapable of signaling even the maximal level of tilt.

In this as in previous studies,3,19 variance and absolute values of VLF, LF, and HF were closely related to age, which differs from the normalized values of LF and HF components.

It is therefore evident that the method of assessing the LF component is a crucial point in spectral methodology. An additional area in which an adequate assessment of LF component appeared of paramount importance for its biological interpretation is its circadian rhythmicity. When LF was analyzed in nu over the 24-hour period,10,27-29 it displayed a clear circadian pattern with a marked nocturnal decrease corresponding to the well known reduction of sympathetic activity. These changes were mirrored by simultaneous increases in HF component, as an expression of the enhanced vagal activity accompanying the largest portion of sleep. The LF component could instead appear unchanged, or even increased during the night,30 if expressed in absolute units, in parallel with the nocturnal rise of variance leading to the questionable31 conclusion that “24-hour LF power is primarily parasympathetically and not sympathetically mediated.”30

On similar grounds, the increase induced by β-adrenergic-blocking agents on the absolute values of LF, due to the increase in total variance induced by the drug, was interpreted by Cook and coworkers32 as indicating that LF component is a marker of vagal activity. Conversely, the sympatholytic action of the drug can be clearly seen by calculating LF in nu or by the LF-to-HF ratio.3,5

The proposed method of quantification3,5,6,9,28,33-35 of spectral components has been applied to a series of human and animal studies. Whenever the signal produced by HRV was adequate and the sympathovagal balance was shifted toward a sympathetic predominance with tilt,3,5,6 moderate hypotension,34 mild physical exercise,26 mental stress,37 or coronary artery occlusion,36 the LF component (in nu) or the LF-to-HF ratio was augmented. The opposite was never observed. This report emphasizes that the spectral methodology, if appropriately used, is a remarkable noninvasive quantitative tool with which one can explore the graded
changes in sympathetic and vagal modulations of sinus node pacemaker activity.

In view of the clinical importance of understanding the neural mechanisms involved in human cardiovascular pathophysiology, it now appears feasible to complement the potentialities of the time domain measurements of HRV, an approach that has already furnished important prognostic information.38-40 with an assessment of the sympathovagal balance as provided by the proposed methodology.

Acknowledgment

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References


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