Autonomic nervous nonlinear interactions lead to frequency modulation between low- and high-frequency bands of the heart rate variability spectrum

Yuru Zhong,1 Yan Bai,1 Bufan Yang,1 Kihwan Ju,1 Kunsoo Shin,2 Myoungho Lee,3 Kung-Ming Jan,4 and Ki H. Chon1

1Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, New York; 2Samsung Advanced Institute of Technology, Yongin-Si, Korea; 3Department of Electrical and Electronics Engineering, Yonsei University, Seoul, Korea; and 4Department of Medicine, Division of Cardiology, Columbia University, New York, New York

Submitted 22 May 2007; accepted in final form 16 August 2007

Zhong Y, Bai Y, Yang B, Ju K, Shin K, Lee M, Jan K-M, Chon KH. Autonomic nervous nonlinear interactions lead to frequency modulation between low- and high-frequency bands of the heart rate variability spectrum. Am J Physiol Regul Integr Comp Physiol 293: R1961–R1968, 2007. First published August 29, 2007; doi:10.1152/ajpregu.00362.2007.—Cardiac sympathetic and parasympathetic neural activities have been found to interact with each other to efficiently regulate the heart rate and maintain homeostasis. Quantitative and noninvasive methods used to detect the presence of interactions have been lacking, however. This may be because interactions among autonomic nervous systems are nonlinear and nonstationary. The goal of this work was to identify nonlinear interactions between the sympathetic and parasympathetic nervous systems in the form of frequency and amplitude modulations in human heart rate data. To this end, wavelet analysis was performed, followed by frequency analysis of the resultant wavelet decomposed signals in several frequency brackets defined as very low frequency (f < 0.04 Hz), low frequency (LF; 0.04–0.15 Hz), and high frequency (HF; 0.15–0.4 Hz). Our analysis suggests that the HF band is significantly modulated by the LF band in the heart rate data obtained in both supine and upright body positions. The strength of modulations is stronger in the upright than supine position, which is consistent with elevated sympathetic nervous activities in the upright position. Furthermore, significantly stronger frequency modulation than in the control condition was also observed with the cold pressor test. The results with the cold pressor test, as well as the body position experiments, further demonstrate that the frequency modulation between LF and HF is most likely due to sympathetic and parasympathetic nervous activities during sympathetic activations. The modulation phenomenon suggests that the parasympathetic nervous system is frequency modulated by the sympathetic nervous system. In this study, there was no evidence of amplitude modulation among these frequencies.

HEART RATE VARIABILITY (HRV) can be used as a noninvasive marker of the sympathetic and parasympathetic influences on the modulation of heart rate (9). It is through efficient interactions between the sympathetic and parasympathetic nervous activities that functions of the cardiovascular system are properly maintained (15). In general, the combined regulations of sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) maintains the constancy of the internal environment of the body, that is, the homeostasis (4). Any disturbances that may cause an imbalance in the homeostasis can and often lead to reciprocal activations of SNS and PNS to facilitate a rapid return to its original state (5). In certain pathophysiological conditions such as the fight or flight, the SNS and PNS can be separately activated, however (5). For example, in response to stress, SNS is preferentially activated to mobilize the source of energy, while in peaceful conditions, PNS is preferentially activated to conserve the source of energy. In these conditions, the activations of both SNS and PNS may attenuate each other to avoid detrimental effect of the overexpression of either one of the nervous activities (5).

Failure of these interactions, that is, imbalance, may lead to sympathetic hyperactivity, promoting the occurrence of life-threatening ventricular tachyarrhythmias, whereas augmented vagal tone exerts a protective and antifibrillatory effect (1). Experimental evidence suggests that myocardial ischemia, acute myocardial infarction, sudden cardiac death, and chronic heart failure all exhibit signs of autonomic function imbalance (11, 13, 17). Consistent with autonomic imbalance, patients who have suffered from a MI have a marked decrease in HRV associated with an increase in sympathetic and a decrease in vagal neural activities (13, 17).

Spectral analysis of either R-R intervals or heart rate (HR) has been widely used in HRV studies, and it has been shown to reflect the dynamics of the two nervous systems. Spectral analysis of human HRV can be divided into three main frequency zones: the spectra below 0.04 Hz are considered to be very low-frequency (VLF) between 0.04 Hz and 0.15 Hz is the low-frequency (LF), and between 0.15 Hz and 0.4 Hz is the high-frequency (HF) band. The LF is found to be mediated by both the sympathetic and parasympathetic nervous influences, and the HF is unequivocally believed to be dominated solely by the parasympathetic nervous system (including respiratory sinus arrhythmias) (1, 24a). The VLF has been speculated to be related to factors other than the autonomic nervous system (ANS) (for example, temperature, hormones, regulation of vascular resistance, and so forth) (3). The ratio of LF components to HF components of the power spectral density (PSD) obtained from linear spectral analysis has been shown to be a useful marker of sympathetic-vagal balance in HRV (24a).

If nonlinear interactions are a common occurrence in maintaining homeostasis and in response to stress, it remains to be determined whether such activities are reduced, enhanced, or missing altogether in many pathological conditions. For exam-
ple, are autonomic imbalances seen in congestive heart failure (11, 13) and myocardial infarction (11, 13), due in part to alterations in any of the three frequency regime’s interactions between the sympathetic and vagus nervous systems? If so, can they be used as a marker for early detection of the progression of pathological states? To adequately answer these questions, we must first develop a way to reliably detect interactions.

Experimental support for the presence of interactions between the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) has come from studies using direct stimulation of the vagal and sympathetic nerves (16, 24). To date, however, computational methods used to detect the presence of interactions between the sympathetic and parasympathetic nervous systems from data taken using noninvasive measurements have had limited success. This may be largely because interactions in physiological systems are nonlinear and nonstationary (6, 23). In addition, noise contamination compounds the complications of developing accurate nonlinear interaction detection algorithms. Further complications arise because interactions between physical mechanisms or systems can lead to a variety of nonlinear phenomena, such as entrainment or synchronization. In cases when synchronization does not occur, interactions between the two systems may reveal themselves in the form of either frequency or amplitude modulation, in which one system may be modulated by the presence of the other system (23). Interactions in the form of either amplitude or frequency modulation are also a consequence of the nonlinear properties of systems.

Entrainment between the sympathetic and parasympathetic nervous systems has not been observed and is unlikely, as the two systems are independent of each other and are designed to counterbalance each other. The most likely scenario for nonlinear interaction is amplitude or frequency modulation between the two systems. To search for evidence of this, we used a wavelet transform followed by the Fourier transform of the oscillating peak frequencies, or amplitudes obtained from the former method, to look for either frequency or amplitude modulation phenomena.

If nonlinear interactions between the sympathetic and parasympathetic nervous activities were indeed found to be present, then we wanted to examine whether the VLF dynamics have any significant relationship with either branch of the autonomic nervous system. The rationale is that if the VLF is indeed not related to the ANS activities as claimed (1), then we should not see interactions (in the form of modulations) of the VLF with either the LF or HF regimes.

Our final aim was to provide evidence that modulations seen are indeed related to the interactions of the two branches of the ANS rather than some other extrinsic factors. This was determined using two different experimental protocols designed to perturb particularly the sympathetic nervous activities, by changing body position from supine to upright and by a cold pressor test. The former is to induce a response so that homeostasis can be obtained, and the latter is to provide a response to stress.

**METHODS**

**Detection of Frequency Modulation and Amplitude Modulation Using Wavelet Scalogram**

The first procedure involves the use of a wavelet scalogram (WS) on the heart rate data to separate the low- and high-frequency oscillatory components. Amplitude modulation (AM) and frequency modulation (FM) are nonstationary processes and require appropriate time-varying spectral techniques such as the WS. Wavelet scalogram was used specifically because of its intrinsic properties of high-frequency resolution in the low frequencies and high time resolution in the high frequencies. These properties are especially advantageous for extracting frequency oscillations in both low- and high-frequency ranges. The wavelet transform of a signal $x(t)$ is obtained as follows (8):

$$ T_s(f,t) = \sqrt{f} \int_{-\infty}^{\infty} x(u) \cdot \Psi \cdot f \cdot (u-t) du $$  \hspace{1cm} (1) $$

where $\Psi$ is a “mother” function, $T_s(f,t)$ are the wavelet coefficients, and $f$ is frequency. The Morlet wavelet function is often selected to analyze periodic components. A simplified expression of the Morlet function is

$$ \psi(\tau) = \pi^{1/4} \exp(j2\pi f_0 \tau) \exp(-\frac{\tau^2}{2}) $$  \hspace{1cm} (2) $$

The time-frequency representation of the energy density of $x(t)$ can be obtained from the wavelet coefficient:

$$ T_s(f,t) \cdot E_s(f,t) = C \cdot f \cdot |T_s(f,t)|^2 $$  \hspace{1cm} (3) $$

where $C$ is a constant determined by the wavelet mother function. $E_s(f,t)$, known as the “scalogram,” is essentially a time-averaged power spectrum. The scalogram $E_s(f,t)$ comprises a frequency vector, $V_t(f)$, for every time point $t$. After a scalogram is generated, the local maxima of the $V_t(f)$ (representing the highest instantaneous frequencies) are detected for every time point within the desired frequency band (e.g., low- and high-frequency bands associated with heart rate spectra). Likewise, maximum instantaneous amplitudes of the low- and high-frequency bands associated with the heart rate spectra can also be extracted. To determine modulation characteristics of the high- and low-frequency oscillations, both extracted instantaneous amplitudes and frequencies are then subjected to the Fourier transform. This last step provides information about all modes involved in the modulation process. All the scalograms in this study were calculated with the wavelet window length set to 4.

**Heart Rate Data Collection**

**Posture change experiment.** Thirteen healthy people (20–40 years old, 8 men and 5 women; mean age 28 ± 5 years) participated in the experiment. The experimental protocol was approved by the human ethics committee at the State University of New York at Stony Brook. The subjects were instructed to breathe at a fixed frequency of 0.2 Hz, aided by a computer-generated sound. The fixed-frequency breathing was adopted because it provides better frequency and amplitude modulation detection. This choice of 0.2 Hz is not that different from the typical spontaneous breathing rate of 0.25 Hz. The depth of breathing was not controlled, as subjects were told to breathe at their normal depth, and also they were told to refrain from any unnecessary body movement during data collection. Twelve minutes of ECG data were collected for both supine and upright postures. Subsequently, detected R-R intervals were converted into 4-Hz instantaneous heart rate signals by cubic interpolation. Each HR data set contained 2,400 data points, which is equivalent to 10 min (transition data between posture change were excluded).

For proper comparison between postures, the HF oscillation time series in the upright position was normalized to unit variance for each subject. The HF oscillations in the supine position were then scaled by the typical spontaneous breathing rate of 0.25 Hz. The depth of breathing was adopted because it provides better frequency and amplitude resolution in the low frequencies and high time resolution in the high frequencies. These properties are especially advantageous for extracting frequency oscillations in both low- and high-frequency ranges. The wavelet transform of a signal $x(t)$ is obtained as follows (8):

$$ T_s(f,t) = \sqrt{f} \int_{-\infty}^{\infty} x(u) \cdot \Psi \cdot f \cdot (u-t) du $$  \hspace{1cm} (1) $$

where $\Psi$ is a “mother” function, $T_s(f,t)$ are the wavelet coefficients, and $f$ is frequency. The Morlet wavelet function is often selected to analyze periodic components. A simplified expression of the Morlet function is

$$ \psi(\tau) = \pi^{1/4} \exp(j2\pi f_0 \tau) \exp(-\frac{\tau^2}{2}) $$  \hspace{1cm} (2) $$

The time-frequency representation of the energy density of $x(t)$ can be obtained from the wavelet coefficient:

$$ T_s(f,t) \cdot E_s(f,t) = C \cdot f \cdot |T_s(f,t)|^2 $$  \hspace{1cm} (3) $$

where $C$ is a constant determined by the wavelet mother function. $E_s(f,t)$, known as the “scalogram,” is essentially a time-averaged power spectrum. The scalogram $E_s(f,t)$ comprises a frequency vector, $V_t(f)$, for every time point $t$. After a scalogram is generated, the local maxima of the $V_t(f)$ (representing the highest instantaneous frequencies) are detected for every time point within the desired frequency band (e.g., low- and high-frequency bands associated with heart rate spectra). Likewise, maximum instantaneous amplitudes of the low- and high-frequency bands associated with the heart rate spectra can also be extracted. To determine modulation characteristics of the high- and low-frequency oscillations, both extracted instantaneous amplitudes and frequencies are then subjected to the Fourier transform. This last step provides information about all modes involved in the modulation process. All the scalograms in this study were calculated with the wavelet window length set to 4.

**Cold pressor test.** Twelve healthy volunteers from the postural study (20–40 years old, 8 men and 4 women; mean age 27.7 ± 4.9
years) participated in the cold pressor experiment. The breathing rate was the same as described earlier, and all ECG data were collected in the upright posture. The protocol consisted of ECG data collection for 6 min in the upright posture followed by 2–3 min with one hand submerged into the cold water at 8–9°C. We chose a temperature higher than most cold pressor tests, as reported in the literature (26, 28), so that subjects were able to submerge their hands in the cold water for at least 2 min. The instantaneous HR data were extracted using the same procedures as described earlier. The same normalization procedure as described for the posture change experiments was applied for the pre- and post-cold pressor experiments.

Statistical analysis. All results are expressed as means ± SD. Statistical analysis was performed using Student’s t-test. A value of $P < 0.05$ was considered significant.

RESULTS

Simulation Example: Detection of FM With Wavelet Scalogram

To test the validity of our approach to determine the presence of frequency modulation, we consider a synthetically generated time series with three frequency bands: VLF (below 0.04 Hz, with center frequency at $f_0$), low frequency (LF: 0.04–0.15 Hz, with center frequency at $f_1$) and high frequency (HF: 0.2–0.4 Hz, with center frequency at $f_2$). In this example, the LF is designed to be modulated by the VLF frequencies, and the HF is modulated by both LF and VLF frequencies. The Appendix provides details about generating an FM signal with the above specifications.

Fig. 1A shows the time tracing of the simulated FM signal, as described in the preceding paragraph. Fig. 1B shows the corresponding scalogram of the signal shown in Fig. 1A, which exhibits VLF activity near 0.02 Hz, LF oscillations centered at $\sim 0.08$ Hz and HF oscillations centered at $\sim 0.3$ Hz. The oscillations seen in both LF and HF bands are due to FM. From Fig. 1B, the highest frequency for each time point within each respective LF and HF band is extracted, and the resultant maximum frequency oscillations within the LF and HF bands are provided in Fig. 1C. The oscillations in these plots represent the FM as designed in the simulation example and exhibit stationary behavior. To determine the frequencies associated with these oscillations, PSD are calculated, and their results are provided in Fig. 1D for the HF and Fig. 1E for the LF bands. Fig. 1D (obtained from the PSD of the high-frequency oscillations in Fig. 1C) shows two distinct frequency bands, centered at 0.02 Hz and 0.08 Hz. On the other hand, Fig. 1E shows a single distinct frequency centered at 0.02 Hz. Therefore, these results suggest that the HF is modulated by both the VLF (0.02 Hz) and LF (0.08 Hz) frequencies, while the LF is modulated by only the VLF (0.02 Hz). These results are the expected outcome, since the data were generated to produce modulation of the LF by the VLF frequencies and HF modulation by both the LF and VLF frequencies.

To quantitatively determine whether the frequency peaks shown in Fig. 1, D and E, represent statistical significance, 20 independent realizations of Gaussian white noise (GWN) time series of the same data length as the simulation example data were generated. Each of these 20 realizations of GWN time series was subjected to the identical data processing, as described for the simulation data. The mean plus two times the standard deviations of the 20 PSDs of the frequency oscillations was used as the statistical threshold. Any spectral power above this statistical threshold line indicates 95% probability that the FM does exist and did not occur by some random occurrence. Note that both the HF and LF oscillation data obtained (the step illustrated in Fig. 1C) for GWN and the simulated example were all normalized to a unit variance prior to computation of PSDs. This procedure allows a comparison between the data of interest and the statistical threshold data obtained via noise sources. Superimposed on Fig. 1, D and E are dotted lines to represent the statistical threshold. The fact that these statistical lines are below the spectral peaks associated with the simulation example data suggests a high probability of the validity of the FM of the VLF and LF on HF, as well as VLF on LF.

We examined the effect of noise on the detection of frequency modulation by adding 0 dB GWN. It was found that even with 0 dB noise (noise variance equal to the signal variance), the statistical threshold line was below the main spectral peaks in Fig. 1, D and E, suggesting the presence of
frequency modulation of the VLF and LF frequencies on HF as well as VLF on LF. Note that a similar procedure can be performed for the detection of amplitude modulation. The only difference is that, in this case, one extracts the maximum amplitude from the wavelet scalogram instead of the maximum frequencies.

**Time-Invariant Power Spectrum-Derived Parameters During Posture Change and Cold Pressor Test**

The results of heart rate, its variance, and its time-invariant power spectra in the LF, HF, normalized low frequency, and normalized high frequency (HFn) domains for all subjects are summarized in Table 1. The comparison is between supine vs. upright positions and control vs. cold pressor test during the upright position. Heart rate, LF, and HF values are statistically different between the two body positions as well as during the cold pressor test. The normalized LF and HF show differences only during the body position test.

**Detection of Frequency Modulation During Posture Changes**

We analyzed heart rate data from 13 subjects in both supine and upright positions with subjects instructed to breathe at 0.2 Hz (12 breaths/min). Heart rate time series data were subjected to the identical data processing procedures as described for the simulation example. Fig. 2A shows representative heart rate data from both postures, and the corresponding power spectra are shown in Fig. 2B. From the LF and HF bands obtained from the scalogram, maximum frequencies at each time point were extracted at each time point. We observe oscillations in Fig. 2, C and D, especially in the HF (centered at 0.23 Hz) and LF (centered at 0.1 Hz) bands for both postures. In Fig. 2, C and D, we observe oscillations that are relatively constant over time in both HF and LF traces. Thus, instead of using another wavelet or time-frequency analysis, we opt to use stationary Fourier transforms of these oscillations to find their exact frequencies. The PSDs of the supine HF and LF oscillations of Fig. 2C are shown in Figs. 2E and 2G, and, likewise, the PSDs of the Fig. 2D upright oscillations are shown in Fig. 2, F and H. Both postures (more pronounced at the upright position) show significant FM of the HF by the LF since the magnitudes of the HF oscillations are greater than the statistical threshold lines (dotted lines) in the LF band. However, no significant FM of the LF by the VLF was found, since the magnitudes of the LF frequency oscillations are lower than the statistical threshold lines in the VLF band. For the group average (n = 13) we only found significant FM of the HF by the LF for the posture study, and the resultant PSD are shown in Figs. 3, A and B. There was no evidence of AM among the VLF, LF, and HF bands for both postures, however.

**Table 1. Comparison of time and frequency domain parameters during supine vs. upright positions and control vs. cold pressor test**

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate</th>
<th>Variance</th>
<th>LF</th>
<th>LFn</th>
<th>HF</th>
<th>HFn</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supine</strong></td>
<td>68.0 (14.0)</td>
<td>25.3 (15.7)</td>
<td>8.2 (6.8)</td>
<td>0.28 (0.17)</td>
<td>21.9 (15.9)</td>
<td>0.72 (0.17)</td>
</tr>
<tr>
<td><strong>Upright</strong></td>
<td>91.5 (9.7)</td>
<td>28.4 (14.6)</td>
<td>17.5 (11.4)</td>
<td>0.64 (0.16)</td>
<td>9.4 (5.9)</td>
<td>0.36 (0.16)</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>89.6 (10.7)</td>
<td>24.1 (13.0)</td>
<td>11.7 (8.7)</td>
<td>0.55 (0.20)</td>
<td>7.4 (3.7)</td>
<td>0.45 (0.20)</td>
</tr>
<tr>
<td><strong>Cold</strong></td>
<td>84.3 (10.1)</td>
<td>37.5 (19.9)</td>
<td>22.8 (23.3)</td>
<td>0.53 (0.22)</td>
<td>15.2 (8.8)</td>
<td>0.47 (0.22)</td>
</tr>
</tbody>
</table>

Values are expressed as means (SD). LF, low frequency; HF, high frequency. LFn = LF/(total power − VLF); HFn = HF/(total power − VLF). *P < 0.05 (by paired Student’s t-test).

Figure 4A summarizes the spectral magnitudes associated with postural positions. There was a statistically significant increase in the LF power and a decrease in HF power when the body position was changed from the supine to the upright position. In addition, there was a significant increase in the FM of the HF by the LF when the body position was changed from the supine to upright position. There was no evidence of AM modulation with the posture experiment.

**Detection of Frequency Modulation During Cold Pressor Experiments**

The cold pressor test was used to demonstrate that the detection of FM can be attributed to the interactions between the SNS and PNS. Fig. 3, C and D show the evidence of FM in both control (upright position) and the cold pressor (upright position) conditions as the PSD magnitudes (solid line) are greater than the statistical threshold lines (dashed lines). In addition, there were elevated PSD magnitudes, and these values are well separated from the statistical threshold line for the cold pressor test compared with the control condition. Note that the cold pressor control experiments were based on different subjects, and data were collected on different days from the data shown for the upright position in Fig. 3B.

Figure 4B summarizes the spectral magnitudes associated with the cold pressor test. Comparing the control to the cold pressor test conditions shown in Fig. 4B, there was a significant increase in HF power and greater evidence of FM with the cold pressor test. There was a nonsignificant increase in LF power from control to the cold pressor test. There was no evidence of AM modulation with the cold pressor test.

While both the SNS and PNS contribute to LF dynamics, the increased FM in HF by LF was most likely due to the activation of the SNS, which is the expected outcome in both experimental groups. The FM was not likely to be induced by the PNS because HF, which represents PNS activities, changed in different directions in the two groups. Therefore, the FM phenomenon can be properly explained by the SNS modulation on PNS, and the modulation effects became stronger with elevated SNS activities.

**DISCUSSION**

A recent work by Sosnovtseva et al. (23), using a double-wavelet approach, has found both frequency and amplitude modulation in renal autoregulation. Similar to their work, in this paper we have employed a wavelet analysis followed by the stationary power spectrum to detect FM and AM in the HRV spectrum. Furthermore, we introduced statistical threshold lines to examine whether oscillations in LF or HF truly represent significant FM or AM and to rule out their random
occurrence. With the aid of the statistical threshold lines, we found significant FM of the HF by the LF bands during both supine and upright positions, as well as with the cold pressor test. In this study, the strength of FM between the LF and HF bands was found to be stronger in upright than supine postures, which was consistent with the well-known phenomenon of the increased sympathetic drive in the upright position (1). Thus, the stronger FM of the HF by the LF may represent greater nonlinear interactions between the parasympathetic and sympathetic nervous systems in maintaining homeostasis. Interactions to maintain homeostasis are a reflection of sympathetic and parasympathetic activities counterbalancing each other, as shown in Fig. 4A.

Increase of LF power with upright posture has been well documented (12, 24a). For example, time-varying spectral analysis based on the use of a complex demodulation method to determine the LF and HF amplitudes of heart rate variability during postural tilt has provided evidence of increased LF amplitude (12). With a cold pressor test, which is known to increase sympathetic nerve activity through a central neural mechanism (10, 22, 28), we consistently found significant FM both before and during cold stress with a considerable increase in the strength of FM with the cold pressor test. The cold pressor experiments were designed to induce higher LF power, and we did find such an increase, although it was not statistically significant. The cold pressor has been shown to increase the LF power and decrease the HF power (28). However, it has also been suggested that the reproducibility of the results with the cold pressor test is highly variable (28), which may be one of the reasons why the previous investigators reported a de-
creased HF power instead of an increase in our experiments. Nevertheless, our results suggest that the presence of greater FM during either the change in body positions or the cold pressor test is most likely due to increased interactions between the SNS and PNS. While the LF is also mediated by the PNS, we believe the FM was not likely to have been induced by the PNS because self modulation is a rare physiological phenomenon.

It is interesting to note that with upright position, the body maintains homeostasis by an activation of SNS and an inhibition of PNS. On the contrary, the cold pressor test causes an activation of both SNS and PNS, such that an increase in PNS is to mitigate hyperreactivity of the SNS. The cold pressor test is an example of fight or flight condition in which rather than maintaining homeostasis, the prevalent action is to protect against initial hyperreactivity of the SNS. Consequently, the PNS is concomitantly increased in the cold pressor test.

The presence of FM is an indication of a particular form of nonlinear interactions between the LF and HF bands. Physiologically, it may represent nonlinear interactions between the sympathetic and parasympathetic nervous systems, which have been well documented in many experimental studies (15, 24, 25). For example, Miyamoto et al. have shown that decreased SNS activity blunts the heart rate response to PNS activation (19). Similarly, a decrease in muscle sympathetic nerve activity after atropine administration has been reported (20). The autonomic imbalance seen in congestive heart failure and myocardial infarction (17, 24a) may also result from abnormal interactions between the sympathetic and vagus nerves. In myocardial infarction, for example, complex nonlinear interactions may exist because elevated sympathetic neural activity often causes depressed vagal activity (13, 14). It has been suggested that one of the causes of the increased sympathetic activation and subsequent decreased vagal activity following acute myocardial infarction is related to activation of cardiac sympathetic afferent fibers (18).

In this study, fixed frequency breathing was adopted to facilitate oscillation detection in the HF regime, as it was...
reported by Pinna et al. (21) that fixed frequency breathing prevents spectral leakage of respiratory mediated autonomic oscillation components into the LF regime from the HF. With spontaneous breathing, extraction of FM values was often difficult due to spectral leakage, as described above. In addition, as we detail below in the study limitation section, in certain subjects, spontaneous breathing resulted in a low spectral power at high frequencies, especially for the upright position. Our fixed breathing rate of 0.2 Hz ensured that there was sufficient spectral power in the HF range. For those subjects who had sufficient power in the HF based on spontaneous breathing, we did find similar results as those found using the fixed breathing. Stronger FM cannot be contributed to by breathing patterns, because Pinna et al. (21) also reported that this breathing protocol does not alter cardiovascular autonomic regulation compared with spontaneous breathing.

We did not find significant amplitude modulations between the LF and HF bands. Detection of amplitude modulation is sensitive to artifacts caused by the time-varying method, measurement noise, and DC components, which may occur due to sudden body motion. Thus, the fact that we were not able to detect the presence of amplitude modulations may not imply that nonlinear interactions in the form of amplitude modulations are not present.

It has been suggested that the dynamics pertaining to the VLF band are related to hormonal and temperature regulations (1). If VLF dynamics are not affected by the ANS, it is likely that evidence of interactions in the form of either FM or AM should not be present. Indeed, we did not find any significant VLF modulation of HF or LF dynamics, indicating that factors contributing to the VLF regime probably do not significantly influence the dynamic properties of the ANS, which is consistent with other findings (1, 24a).

It should be noted that although we have adopted a wavelet method to extract amplitude and frequency modulations, other time-varying methods, such as time-varying complex demodulation method (27) and smooth pseudo Wigner-Ville method (7), are also applicable. One criterion for choosing a time-varying method is that it should have sufficiently high time and frequency resolution to obtain either frequency or amplitude modulations. Thus, the widely used short-time Fourier transform method, which has one of the poorest concomitant time and frequency resolutions, may not be the ideal method to utilize.

Study Limitations

Although we have shown that the HF oscillation is a useful tool in quantifying the FM effect between the LF and HF bands, there are some limitations in its applicability. When HF power is low, it becomes difficult to obtain accurate HF oscillations from a scalogram. To avoid this, we used the fixed frequency breathing method. It should be noted, however, that our choice of a fixed-frequency breathing rate of 0.2 Hz is close to the spontaneous breathing frequency of most of the subjects studied.

Conclusions

In this study, we have detected nonlinear interactions in the form of FM between LF and HF bands. Using two postural positions and the cold pressor test, we suggest that the FM most likely represents nonlinear interactions between the sympathetic and parasympathetic nervous systems. Quantification of nonlinear interactions has been aided by the use of a wavelet analysis, which is ideal for detecting time-varying dynamics. Finally, verification of nonlinear interaction detection in the form of FM was confirmed using a statistical significance threshold level, which we have developed. The approach could be potentially used as a noninvasive method to determine whether autonomic imbalances seen in many cardiac diseases are partly due to abnormal interactions between the sympathetic and parasympathetic nervous activities.

APPENDIX

Frequency and Amplitude Modulation Simulation Example

FM, FM involves oscillations in which a particular frequency or frequency band varies according to another frequency or frequency bands. Let \( f_1 = 0.02, f_2 = 0.08 \), and \( f_3 = 0.03 \) be defined as the center frequencies of the frequency bands VLF, LF, and HF, respectively. The frequency in the LF band [denoted as \( f_2(t) \) (Eq. A1)] changes according to rhythms defined by the VLF, and the HF band [denoted as \( f_3(t) \) (Eq. A2)] oscillates according to both LF and VLF:

\[
f_2(t) = g_1 \sin(2\pi f_2 t) + f_1 \tag{A1}
\]

\[
f_3(t) = g_2 \sin(2\pi f_3 t) + g_3 \sin(2\pi \int_0^t f_2(t)dt) + f_2 \tag{A2}
\]

The simulation signal \( y(t) \) with FM phenomenon can be obtained with Eq. A3.

\[
y(t) = A_0 \sin(2\pi f_3 t) + A_1 \sin(\int_0^t f_1(t)dt)
\]

\[
+ A_2 \sin(2\pi \int_0^t f_2(t)dt)
\]

where the constants \( g_1, g_2, \) and \( g_3 \) signify the strength of FM, and \( A_0, A_1, \) and \( A_2 \) characterize the contribution of the VLF, LF, and HF bands, respectively, to the output signal. For our simulation example, the following parameter values were used: \( g_1 = g_3 = 0.03, g_2 = 0.01, \) and \( A_0 = A_1 = A_2 = 5 \).

AM, AM is a phenomenon where the amplitude of one frequency band oscillates according to another frequency band. The amplitude in the LF band [denoted as \( B_1(t) \)] is modulated by VLF (Eq. A4), and the amplitude in HF band [denoted as \( B_2(t) \)] is modulated by both VLF and HF, as shown in Eq. A5.

\[
B_1(t) = g_1 \sin(2\pi f_1 t) + B_1 \tag{A4}
\]

\[
B_2(t) = g_2 \sin(2\pi f_2 t) + g_3 \sin(2\pi f_1 t) + B_2 \tag{A5}
\]

The simulation signal with AM phenomenon, \( y(t) \), can be obtained with Eq. A6.

\[
y(t) = B_0 \sin(2\pi f_0 t) + B_1(t) \sin(2\pi f_1 t) + B_2(t) \sin(2\pi f_2 t) \tag{A6}
\]

where \( g_1, g_2, \) and \( g_3 \) are the strength of AM and \( B_0, B_1, \) and \( B_2 \) characterize the contribution of the VLF, LF, and HF bands, respectively, to the output signal.

GRANTS

This work was supported by a research grant from National Institutes of Health HL-76358.
REFERENCES