Bispectrum and Bicoherence for the Investigation of Very High Frequency Peaks in Heart Rate Variability

E Toledo, I Pinhas, D Aravot, S Akselrod

Tel Aviv University, Tel Aviv, Israel

Abstract

Recently, we reported the occurrence of Very High Frequency (VHF) peaks in the HR and BP spectra in heart transplant (HT) patients. In this study, we apply the bicoherence function, which provides an estimate of correlation between 3 spectral peaks, thus allowing to determine the relations between the VHF peaks and other peaks. A statistical approach was used to determine a threshold, which discerns true bispectral peaks from spurious ones for any required level of significance.

Twenty five recordings of HR, BP and respiration were obtained from 13 male HT patients. Extensive arrhythmias prevented spectral analysis in 8 recordings. VHF peaks were found in the HR and BP in 9 recordings. We found 2 types of VHF peaks: 1) harmonics of respiration, and 2) peaks totally uncorrelated with respiration. Four recordings exhibited type 1 peaks, 1 recording had only type 2 peaks and 4 recordings had both types. The nature of the VHF peaks remains to be resolved.

1. Introduction

Spectral analysis of physiological signals is a powerful tool in the study of oscillatory systems, and especially in the study of autonomic control over the heart. The typical spectral pattern of both HR and BP displays 2 main region of power: the Low Frequency (LF) peak, centered at about 0.1 Hz, and High Frequency (HF) peak, centered at the respiratory frequency. Both peaks are associated with the activity of the autonomic nervous system (ANS). Yet, it has been shown that remnants of those peaks may still exist in cases of full autonomic denervation. This is the case for either pharmacological blockade or surgical denervation [1,2], as in the case of heart transplant (HT) patients. In these "denervations", the spectral pattern of HR and BP resembled the typical pattern, yet with markedly reduced power compared to normal subjects. The remnant HF component in HT patients has been attributed to the mechanical effect of changes of intrathoracic pressure due to respiration on the SA node [2]. The LF component has been shown to correlate with the extent of sympathetic reinnervation [3].

Recently, we reported the finding of Very High Frequency (VHF) peaks in the power spectrum of HR and BP obtained from heart transplant (HT) patients [1,4,5]. In those patients, the VHF peaks appear at frequencies well above the respiratory frequency, up to 2.5 Hz. An example of the VHF peaks is shown in Figure 1. In [5], we showed that the VHF peaks are not artifactifactual. The main evidence substantiating the validity of this phenomenon is the occurrence of the VHF peaks in both HR and BP signals, each of which obtained by independent analysis and by different methods. We hypothesized that the occurrence of VHF peaks in the power spectrum of HR and BP reflects the lack of vagal innervation. This hypothesis is based upon the assumption that the VHF peaks are harmonics of the respiratory frequency.

Spectral analysis, while able to describe and characterize those peaks, does not provide any information about the inner structure of the spectrum. This analysis is unable to disclose the correlation between different spectral peaks. Therefore, it is impossible to use the information provided by the spectral analysis to understand the origin of the VHF peaks. This drawback stems from the loss of phase information. Consequently, power spectral analysis fails to fully describe nonlinear systems, whose spectral patterns are complex.

In this study, we analyze the VHF peaks within the framework of the Higher Order Statistics approach, and characterize the statistical relations between the various HR and BP oscillations.

2. The bispectrum and bicoherence

2.1. Definitions

The 3rd order cumulant of a square integrable stationary signal $s(t)$ with zero mean, is defined as the 3rd order moment [6]:

$$c(t_1,t_2) = \mathrm{E}\{s(t_1)s(t_2)s(t_1+t_2)\} \tag{1}$$

The bispectrum of a $s(t)$ is defined by:

$$C(\omega_1,\omega_2) = \iint c(t_1,t_2)\mathrm{e}^{-i(\omega_1 t_1+\omega_2 t_2)}\,dt_1 dt_2 \tag{2}$$

A consistent and unbiased estimator of $C(\omega_1,\omega_2)$ can be computed similarly to the Welch Periodogram. The signal is divided into N_0 segments (with or without overlapping), the segments are multiplied by a window $W[l]$ and the Fourier transform of each segment is computed:

$$S_k(\omega)=\sum_{l=1}^{M} s[l+kM]\cdot W[l]e^{i\omega l}$$

where M is the length of the segment. The estimator for the bispectrum is then:

$$\hat{C}(\omega_1,\omega_2)=\frac{1}{N_0}\sum_{k=0}^{N_0-1} S_k(\omega_1)S_k(\omega_2)S_k^*(\omega_1+\omega_2) \quad (3)$$

This estimator is unbiased:

$$E\,\hat{C}(\omega_1,\omega_2)=C(\omega_1,\omega_2)$$

and consistent:

$$\lim_{N\to\infty}\hat{C}(\omega_1,\omega_2)=0$$

The bispectrum provides information about the 3rd order statistics of the signal, and therefore about its nonlinearities. Higher order polyspectra, which can be assessed similarly to Eq. (3), provide information about higher order cumulants, and reflect even higher order statistics.

The bispectrum provides a measure of the statistical correlation between 3 spectral peaks, and therefore about the coupling between the 3 peaks. Yet, the bispectrum has a drawback: its value depends on the power of the spectral peaks. Therefore, weakly coupled but strong oscillations would result in the same bispectral value as strongly coupled but low power oscillations. The bicoherence function, which resembles the coherence function not only by name, is a normalized measure of the correlation between the peaks:

$$\hat{B}(\omega_1,\omega_2)=\frac{\hat{C}(\omega_1,\omega_2)}{\left|\hat{S}(\omega_1)\hat{S}(\omega_2)\hat{S}(\omega_1+\omega_2)\right|^{1/2}} \quad (4)$$

where $\hat{S}(\omega)$ is the estimated power spectrum of the signal. Small values of the bicoherence indicate weak correlation and large values indicate strong correlation between the 3 spectral peaks.

Note, however, that unlike the coherence function, the bicoherence can assume values larger than 1 in some cases. For that reason, this kind of normalized bispectrum is referred to as "skewness" by several researchers, while

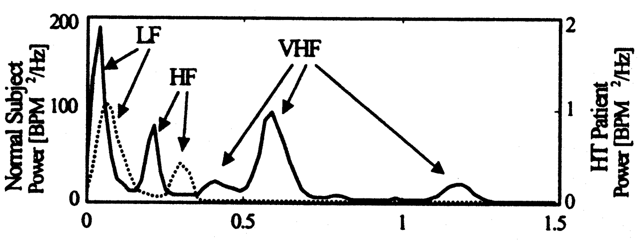

Figure 1: HR spectra of a normal subject (dotted) and HT patient (solid). Note the 2 order-of-magnitude difference in the ordinate, and the presence of VHF peaks in the spectrum of the HT patient.

the term bicoherence is defined differently by those researchers, in a way, which limits its value to 1. However, we use the normalization scheme described in Eq. (4) for reasons that will be clarified in the following section.

Applying the bicoherence to real and noisy data results in many spurious bispectral peaks in the (ω_1,ω_2) plain due to noise. Extracting the "true" peaks, i.e. those reflecting coupled oscillations, is not straightforward. This problem is also encountered when analyzing a system using the coherence function. In the latter case, a threshold of 0.5 is typically used to discern peaks, which represent coupled oscillations from spurious peaks caused by noise. This threshold is arbitrary and its value has been criticized.

In this work, we applied the approach suggested by Haubrich [7] to discriminate real bispectral peaks from spurious ones. The principle of this method is to consider the question of a bispectral peak being a real one within the framework of statistical hypothesis testing. The null hypothesis in this case is that the analyzed signal is a Gaussian random process. We can reject of accept this hypothesis, depending on the value of the bicoherence. Determining the threshold using this approach provides an objective and quantitative method to differentiate real from spurious peaks. However, the statistical properties of the bicoherence, under the assumption of the null hypothesis, must be known. Therefore, we focus on the statistical properties of the bicoherence of Gaussian stochastic processes.

2.2. Statistics of the bicoherence

It was shown that the magnitude of the bicoherence is asymptotically χ^2 distributed with 2 degrees of freedom, in the case of non-overlapping, rectangular windowed segments [7]:

$$\xi\cdot\left|\hat{B}(\omega_1,\omega_2)\right|^2\sim\chi_2^2,\quad \xi=2N_0 \quad (5)$$

The factor ξ depends only on the number of segments used. Therefore, a threshold can be derived from this observation, for any significance level. For example, by setting the threshold to $\sqrt{9.2/\xi}$, we set a 1% significance level, i.e. the probability that the null hypothesis holds for a peak higher than this threshold is less than 1%. Note, that with longer traces, which result in increased N_0, and thus increased value of ξ, it is possible to discern lower values of bicoherence from the noise.

Yet, for a given signal, the number of segments N_0 is determined by the length of the segments. This length determines the spectral resolution. Increasing N_0, while keeping the total number of data points constant, results in a lower threshold for a given significance level. That means weaker coupling may be differentiated from noise. Therefore, one has to compromise between spectral resolution and the minimal level of coupling that can be detected. Using overlapping segments enables us to apply a lower threshold while preserving spectral resolution to some extent. However, in the case of overlapping segments, some data points are included in 2 (or more) segments and as a result, the segments become statistically dependent. Therefore, the simple linear dependency of the factor ξ on N_0 is no longer valid.

We used numerical simulations to verify that the bicoherence is indeed χ^2 distributed and to assess the factor ξ in the case of overlapping segments.

2.3. Simulations

White Gaussian Noise signal of 20,000 samples long was generated and then divided into shorter segments. We used window lengths of 64–2048 points. Overlap ranged within 0–80%. The number of bispectral points varied for each window length. Then we repeated the simulation for each window length until at least 150,000 bispectral points were accumulated, in order to provide an accurate estimate of the statistical properties of the bispectrum.

The bicoherence function was calculated using (4) and histograms of amplitude were derived. We found that the bicoherence was χ^2 distributed with 2 degrees of freedom for all window sizes and all percentages of overlapping. We found that a complex dependency of the factor ξ on the number of segments N_r. Figure 2 shows the factor ξ versus the number of segments N_r for several window lengths. The relation is clearly nonlinear.

We found that ξ has the following dependency on the number of overlapping segments N_r and the number of segments N_0 when no overlapping is allowed:

$$\xi = 4.01 \cdot \frac{N_0}{1+(N_0/N_r)^2} \qquad (6)$$

Note that $N_r \geq N_0$ and that in the limit $N_r = N_0$ Eq. (6) reduces into $\xi = 2N_0$, as in Eq. (5). Using overlapping segments thus has the same effect as using longer data traces.

The distribution of $\left|\hat{B}(\omega_1,\omega_2)\right|^2$ is fully determined by introducing Eq. (6) into Eq. (5), in the case of overlapping segments. Therefore, a threshold can be derived for any desired significance level, for every window length (in the computed range) and any overlap.

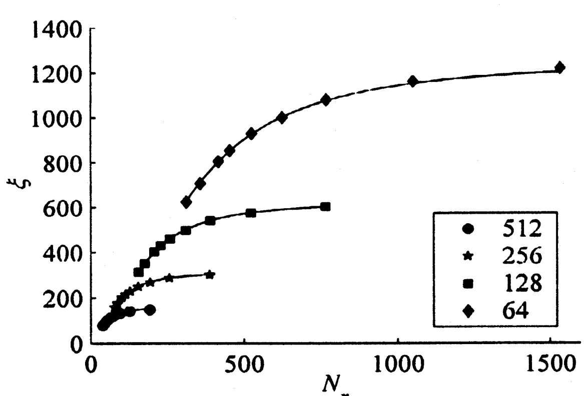

Figure 2: The factor ξ vs. the number of segments N_r. The fitted curve is shown in solid line. The various window lengths are indicated by different markers.

3. Experimental data set

The recordings were obtained from 13 male HT patients (age: 28-68, mean=52±12 years). All patients received immunosuppressive therapy. In this group, 25 recordings were performed at Times-After-Transplant (TAT) in the range 0.5-62.5 months: 5 subjects were recorded once, 6 subjects were recorded twice and two subject were recorded 4 times, at different TAT. None of the subjects had any signs of graft rejection prior to any recording session. The control group consisted of 14 normal male subjects (age 28-59, mean=41±6 years).

The subjects were monitored continuously in 3 different postures: 45 min in supine position, 5 min during upright standing and 10 min while sitting. The transitions between postures were metronome paced, and lasted 10 sec. The recordings began following 10 min of supine rest. Lead I ECG (Biopac), continuous BP (Finapres-Ohmeda) and respiration (Respitrace) were acquired directly to a computer at a rate of 500 Hz.

Following very accurate R-wave detection, all signals were low-pass filtered, decimated to 10 Hz, and only then analyzed. Before performing the bispectral analysis, the HR trace was high pass filtered, applying a nonlinear filter: dividing the signal into 50 sec epochs and removing the linear trend from each epoch. This filter reduced the effect of the non-stationarity, which tends, in HT patients, to obscure the structure of HRV spectrum. Such filter is rarely required in normal subjects, in whom HRV is much higher and hence less susceptible to be affected by non-stationarity. Eight recordings experienced extensive arrhythmias; these recordings were therefore not submitted to spectral analysis.

4. Application to the real data

Both BP and HR signals resulted in the typical LF and HF peaks, noting however that the power of these peaks in the HT patients was markedly below normal values. This spectral structure existed for all HT subjects [1].

Spectral analysis of HR and BP in HT patients revealed an intriguing phenomenon: spectral peaks at frequencies well above the respiratory frequency. Such VHF peaks were found in 9 recordings. No significant VHF peaks were found in the spectrum of the respiration signal.

The bicoherence during supine position was computed for the HR and BP traces. Bispectral peaks, for which the bicoherence was lower than the threshold (computed using Eqs. (5) and (6)) were discarded. Examination of the bicoherence of the traces which exhibited VHF peaks, revealed two types of peaks. VHF peaks of the first type were plain harmonics (second and higher) of the respiratory frequency, i.e. $\hat{B}(\omega_{resp},\omega_{resp}) \gg 0$. The second type VHF peaks were peaks in the spectra of HR and BP, which were uncorrelated to the respiratory frequency. Figure 3 displays the power spectrum and bicoherence of a HR trace, which exhibited both types of VHF peaks. The spectral peaks are labeled by V_1–V_4 and the bicoherence peaks are labeled by Greek letters. V_1 is the second harmonic of HF, indicated by bispectral peak α. Peak V_2 is uncorrelated with LF, HF and V_1. Any correlation between V_2 and one of the lower-frequency peaks would result in a bispectral peak somewhere between α and γ. The peak V_3 results from coupling of HF and V_2, indicated by β. V_4 is the second harmonic of peak V_2, indicated by bispectral peak γ. Therefore, peak V_1 belongs to first type VHF peaks, while peaks V_2 and V_4 are second type VHF peaks. This specific example displayed additional peaks at even higher frequencies (omitted here). Four recordings exhibited the first type of peaks, 4 recordings exhibited both first and second type, and one recording exhibited only the second type.

The second type VHF peaks appeared with clearly significant power, and in some cases, with more power than the HF peak (e.g. peak V_2 in Figure 3). We found no correlation between the incidence of VHF peaks and time after transplantation, or with any of the parameters described in [1].

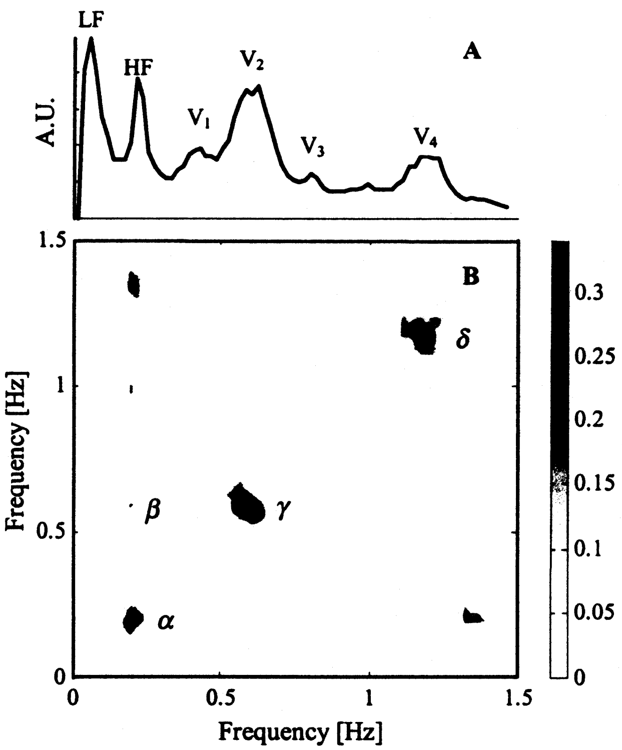

Figure 3: HRV Power spectrum (A) and the corresponding bicoherence (B), displayed as gray scales, of an HT patient. The HR and BP of this patient exhibited both types of VHF peaks.

5. Conclusions

Bispectral analysis using the bicoherence has proved to be valuable in the study of nonlinear correlation in HR and BP signals. The main result of this study is the finding of two types of VHF peaks in the HR and BP of HT patients. Indeed, the assumption that the VHF peaks are harmonics of the respiratory frequency [5] was confirmed in 8 (out of 9) cases. However, not all VHF peaks are harmonics of respiratory frequency, as reflected by the second type peaks. The existence of a second type of VHF peaks, uncorrelated with respiration, is remarkable. Although our analysis ruled out any correlation between the HF peak and the second type VHF peaks, it is still possible that the respiratory system is complexly involved in the creation of those peaks. One such possibility is that the VHF peaks result from physiological aliasing of high harmonics of respiration: the SA node is affected mechanically by respiration, however due to the relatively low sampling rate of the SA node (HR≈1.5 Hz), higher harmonics of respiration (f>0.75 Hz) are aliased as lower frequency peaks. Those oscillations are then reflected in the BP. Another possibility, even more exciting, is that those peaks are the manifestation of a new, yet unknown cardiovascular control mechanism.

Acknowledgements

This work was supported by grant no. 447-98 of the Israeli Science Foundation and the Welcome foundation.

References

1. Toledo E, Pinhas I, Almog Y, Aravot D, Solange A. Functional Restitution of Cardiac Control in Heart Transplant Patients. Submitted to Am J Physiol.
2. Bernardi L, Salvucci F, Suardi R, Solda PL et al. Evidence for an intrinsic mechanism regulating heart rate variability in the transplanted and the intact heart during submaximal dynamic exercise? Cardiovasc Res 1990;24:969-981.
3. Kingwell BA, Thompson JM, Kaye DM et al. Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. Circulation 1994;90:234-240.
4. Toledo E, Pinhas I, Aravot D, Akselrod S. Evolution of Compensatory Cardiovascular Control Mechanisms in Heart Transplant Subjects. Comp in Card 2000;27:1-4.
5. Toledo E, Pinhas I, Aravot D, Akselrod S. Very High Frequency Oscillations in the Heart Rate and Blood Pressure of Heart Transplant Patients. Submitted to IEEE Trans Biomed Eng.
6. Nikias CL, Petropulu AP. Higher-order spectral analysis. NJ: Prentice-Hall, 1993.
7. Haubrich RA. Earth Noise, 5 to 500 Millicycles per Second. J Geophys Res 1965;70:1415-1427.

Address for correspondence:
Prof. Solange Akselrod, Medical Physics, School of Physics, Tel-Aviv University, P.O. Box 39040, Tel Aviv 69978, Israel
Email: solange@tau.ac.il