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Nonlinear measures on heart rate variability: A clinical tool or not?

To the Editor:

Spectral analysis on heart rate variability (HRV) has been a widely accepted linear method in the assessment of autonomic nervous system (ANS) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), in which HRV reveals a delicate balance between the two antagonistic parts of ANS: sympathetic and parasympathetic activities. Recently, Yeh et al. (2009) used a nonlinear method, i.e., detrended fluctuation analysis (DFA) developed by Peng et al. (1995), to analyze HRV in late pregnant women. And their main finding, published in this journal, is that detrended fluctuation scaling exponents might be new and independent measures of HRV in late pregnancy, in addition to those conventional linear measures. Hence, the underlying physiological meanings of these scaling exponents in pregnant women are still unclear. Owing to their results, we are motivated to reconsider this topic "Nonlinear measures on heart rate variability: A clinical tool or not?".

It is well known that DFA is one of the powerful methods to detect self-similar scaling exponents (i.e., nonlinear indices) embedded in nonstationary biomedical signals. The use of nonlinear indices is usually justified by considering them as numerical indices, which are supported by clinical studies in large-scale database. However, in fact, the clinical interpretation of changes in these indices is quite difficult. One of the possible reasons is that they compress cardio-respiratory dynamics including heart rate, blood pressure, and respiration rate in a single numerical index, thus it is not easy to determine physiological relationships between the change in the index and the physiopathological causes. Nevertheless, to discover the clear physiological meaning of these nonlinear indices is of fundamental importance. Ursino and Magosso (2003) developed a detailed lumped parameter model (LPM) which contains the interconnection of ANS (sympathovagal activity) and non-autonomic components (peripheral resistance). According to numerical results of LPM (Rojo-Alvarez et al., 2007), it has been known that an increase of sympathetic tone or a decrease of vagal tone can significantly enhance the short-term $\alpha1$ index (determined from 4 to 11 beats). In addition, the long-term $\alpha2$ index (>11 beats) can be significantly affected by the decrease of peripheral resistance.

There is a more natural way to realize the physiological meaning of nonlinear indices based upon traditional spectral analysis on HRV. Usually the spectrum is broken into three regions for analysis. (a) The very low-frequency (VLF) region covers from 0.000 to about 0.040 Hz. This region cannot usually be resolved but would be related with long-term factors such as thermoregulation of heart rate. (b) The low-frequency range (LF, 0.040–0.150 Hz) often shows a peak at about 0.100 Hz, the origin of which is still unclear. Increased LF power may indicate sympathetic activation. (c) The high-frequency region (HF, 0.150–0.400 Hz) covers rapid variations in heart rate due to vagal activity. It is known that in the rest status heart rate for normal subjects is 60–100 bpm, then one heartbeat needs 0.6–1 s. Therefore, the time characteristic for $\alpha1$ index covers from 2.4 s to 11 s, and the associated frequency range would be 0.417–0.090 Hz which is located in both of HF and LF bands. This is why the sympathovagal activity is strongly related to $\alpha1$ index. Accordingly, $\alpha2$ index covers LF and VLF bands. This simple statement is consistent with the result by Willson et al. (2002). Compared to the previous physiological/theoretical findings of Ursino and Magosso (2003), Rojo-Alvarez et al. (2007), and Willson et al. (2002), the conservative working hypothesis to reveal the physiological meaning of nonlinear indices would be that $\alpha1$ index should reflect the result of the sympathovagal balance (or imbalance), and $\alpha2$ index is still unclear at present.

It is well known that low-/high-frequency power ratio (LHR) is a well-accepted index to describe the sympathovagal activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Intuitively, $\alpha1$ index should be strongly correlated with LHR. This concept we think is correct in principle. In postural-change experiments (Montano et al., 1994; Malliani et al., 1997) people have realized that sympathetic activity will be enhanced in the standing position because of gravitation. Hence, decreasing sympathetic activity would be expected in the supine position. Increasing (decreasing) sympathetic activity indicates low-frequency oscillations (LFOs) of HRV will be enhanced (reduced), thus LHR should be correspondingly increased (decreased). In the viewpoint of time series, LFOs describe the characteristic of positive correlations embedded in HRV data. In fact, DFA is an outstanding method to detect positive (or negative) correlations in biomedical signals, which can be expressed through the monofractal scaling exponent, α index. Therefore, it is not surprising that there is a mathematical relation between DFA and spectral analysis (Peng et al., 1995). It is known that the spectral density can be approximately expressed as a power-law distribution $f^{-\beta}$, where β is an exponent and α and β indices obey the following relation:

$$\beta = 2\alpha - 1 \quad (1)$$

For example, when Gaussian white noise of the flat band is considered, $\beta = 0$ and, therefore, $\alpha = 0.5$. LHR in mathematics should be equal to 0.44 (LF, 0.040–0.150 Hz; HF, 0.150–0.400 Hz). If β (α) is larger than zero (0.5), it indicates positive correlations are predominant in the original data, thus LHR will be increased over 0.44. However, it needs more careful treatments in clinical applications. As mentioned above, $\alpha1$ index would be responsible for the sympathovagal balance (or imbalance) and the frequency characteristic for $\alpha1$ index covers from 0.090 Hz to 0.417 Hz, which does not occupy the entire LF band and finally leads to the uncertainty for spectral-power calculations. Owing to that, LHR should be defined in a new frequency-domain rather than a traditional one. This procedure might give the correct relation between $\alpha1$ index and LHR. Our interpretation is valid to address why the study of the correlation coefficient between $\alpha1$ index and LHR in previous articles, see the text in the paper of Yeh et al. (2009), has not obtained consistent results. Of course, in practical aspects it still has a space to discuss the uncertainty embedded in LHR (see below).

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In mathematics spectral analysis is valid when time series exhibits the stationary characteristic. HRV, in fact, is a result from nonstationary cardio-respiratory processes, therefore, a crucial procedure to be simultaneously performed is to obtain respiratory rate in order to assess its synchronization with HF component. However, when the frequency of respiration is decreased and close to the LF rhythm in such a way that HF and LF merge into one single dominant oscillation. Thus, it is difficult to define LHR in this case. Although using controlled breathing is a way to maintain the frequency of respiration above the LF range, nevertheless, this is not physiological breathing and it can artificially shift the sympathovagal balance towards vagal predominance. In short, it would not be surprising that previous studies, cited in the paper of Yeh et al. (2009), on correlation results between LHR and $\alpha1$ index with/without controlled breathing have not given consistent conclusions. The possible way to overcome the present situation we suggest should measure respiration as well as HRV data simultaneously, which would be helpful to accurately define LHR rather than traditional usage in spectral analysis.

Although nonstationary cardio-respiratory processes will increase difficulties to realize the physiological basis of DFA and its relation to linear HRV measures, there is a mathematical relation between DFA and spectral analysis as simply described above. Thus, it is incorrect/inappropriate to describe that DFA scaling exponents will not correlate with most HRV measures in the theoretical point of view, by which as well as previous inconsistent results Yeh et al. (2009) claimed that $\alpha1$ index might be a new and independent measure of HRV, in addition to the conventional time and frequency-domain HRV measures.

In this letter, we try to give a better understanding about the relation between $\alpha1$ index and LHR through various viewpoints, including physiological/theoretical models and clinical symptoms during the postural change. We think nonlinear measures that resulted from sophisticated maths would become powerful tools for clinical applications. However, the understanding of the physiological basis of nonlinear measures would play a crucial role for future applications (Shiau, 2009), rather than considering them as numerical indices supported by clinical studies in large-scale database.

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