Fractal dimension and approximate entropy of heart period and heart rate: awake versus sleep differences and methodological issues

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Abstract

1. Investigations that assess cardiac autonomic function include non-linear techniques such as fractal dimension and approximate entropy in addition to the common time and frequency domain measures of both heart period and heart rate. This article evaluates the differences in using heart rate versus heart period to estimate fractal dimensions and approximate entropies of these time series.

2. Twenty-four-hour ECG was recorded in 23 normal subjects using Holter records. Time series of heart rate and heart period were analysed using fractal dimensions, approximate entropies and spectral analysis for the quantification of absolute and relative heart period variability in bands of ultra low (< 0.0033 Hz), very low (0.0033–0.04 Hz), low (0.04–0.15 Hz) and high (0.15–0.5 Hz) frequency.

3. Linear detrending of the time series did not significantly change the fractal dimension or approximate entropy values. We found significant differences in the analyses using heart rate versus heart period between waking up and sleep conditions for fractal dimensions, approximate entropies and absolute spectral powers, especially for the power in the band of 0.0033–0.5 Hz. Log transformation of the data revealed identical fractal dimension values for both heart rate and heart period. Mean heart period correlated significantly better with fractal dimensions and approximate entropies of heart period than did corresponding heart rate measures.

4. Studies using heart period measures should take the effect of mean heart period into account even for the analyses of fractal dimension and approximate entropy. As the sleep–awake differences in fractal dimensions and approximate entropies are different between heart rate and heart period, the results should be interpreted accordingly.

Introduction

Non-invasive studies of cardiac autonomic function are very useful in several different fields such as cardiology, physiology, pharmacology, psychology and psychiatry. These studies have shown great promise in understanding cardiac mortality in patients with heart disease and also apparently healthy subjects as well as elucidating cardiac autonomic function in anxiety disorders such as panic disorder [1–11]. One such non-invasive technique is a measure of heart period (HP) (R–R interval in ms) or heart rate (HR) (beats/min) variability, and most studies...
use the former measure. The time series data for HP or HR can be obtained in the laboratory using an electrocardiographic monitor or outside the laboratory using a Holter recorder, to obtain 24-h time series. Both HR and HP distributions frequently deviate from the normal distribution. Graham [12] has shown that HR may have a slight advantage in infants for physiological research.

Spectral analysis of short-term HP or HR time series reveals a high-frequency peak (HF: 0.15–0.5 Hz), related to respiratory sinus arrhythmia, a low-frequency peak (LF: 0.04–0.15 Hz), related to sympathetic, vagal and baroreceptor mechanisms, and a very-low-frequency peak (VLF: 0.01–0.04 Hz), related to thermoregulatory and peripheral vascular mechanisms [2,7]. As the time series of HR are not linear, some investigators have stressed the importance of non-linear techniques to quantify HR variability [9].

Several recent reports discuss the problems of using HP versus HR in various time and frequency domain analyses [13–19]. Niklasson et al. [13] have shown considerable differences between measurements based on beat-by-beat HR and measurements based on HP. They concluded that analysis directly based on R–R intervals could give biased results with respect to the underlying autonomic activity. Jannsen et al. [14] compared interbeat interval series, spectrum of counts and instantaneous HR series and concluded that spectra were incomparable without normalization of the tachogram with respect to HR. Castiglioni [16] has reported extensively on the differences between HR and HP and emphasized that the link between HR and HP is non-linear, and that this non-linearity causes discrepancy between HR and HP variabilities. Castiglioni also suggests that logarithmic transformation of HR and HP time series solves this problem.

Several investigators have stressed the importance of non-linear techniques such as fractal dimension (FD) and approximate entropy (APEN) to analyse HR time series, as these series are essentially non-linear in nature [20,21]. There are several ways to determine FD, which measures the space-filling propensity and complexity of the time series [22]. APEN quantifies the regularity in time series data. This measures the logarithmic likelihood that runs of patterns that are close remain close on the next incremental comparisons, and the higher the entropy value the more random the time series [21]. In this study, we evaluated the differences in the analyses of FDs and APENs between the awake and sleep time series of instantaneous HR and HP using data from 24-h Holter records. We also evaluated the effects of linear detrending on the quantification of FDs and APENs of HR and HP.

Methods

Twenty-three normal subjects [14 females and 9 males, 35.4 ± 10.2 years of age (mean ± S.D.)] participated in this study. Values were expressed as means ± S.D. throughout the study. The study was approved by the Institutional Review Board at the Wright State University School of Medicine. A signed informed consent was obtained from all participants. The subjects were physically healthy with no history of hypertension and their routine blood chemistry and ECG did not show any significant abnormalities. The subjects did not take any medication for at least 4 weeks before the study except for occasional non-opioid analgesics. Two of the subjects were smokers. This investigation accords with the principles outlined in the Declaration of Helsinki.

Data collection

Holter records were obtained by using Delmar Cardiographs over a 24-h time period using standard procedures. Subjects were asked to keep a diary of various activities during the procedure; most importantly, when they went to sleep and when they woke up.

Analysis of the data

The Holter records were scanned by one of the investigators using the Delmar 750 A system. The ECG was sampled at 256 Hz for the analyses. The R–R (interbeat) interval data were downloaded to a PC using a custom-developed program. These data were edited using software that eliminated any glitches due to premature ventricular beats. We used a similar method to that used by Huikuri et al. [2]. An R–R interval was interpreted as a premature beat if it deviated from the previous qualified interval value by more than a tolerance level of 30%. These beats were eliminated and the resulting gaps were filled with an average value in the immediate neighbourhood. All data sets had more than 95% qualified beats. The edited time series data were later sampled at 2 Hz using the method of Berger et al. [23] to obtain instantaneous HR. This stepwise continuous instantaneous HR signal maintains an amplitude equal to the reciprocal of the current R–R interval, and the convolution of the HR signal with the rectangular window has the effect on the power spectrum of multiplication by a low-pass filter [23]. Using a 2-Hz sampling rate would allow an accurate estimation of the power spectrum up to 0.5 Hz.

From these 24-h time series of instant HR and HP data, we analysed a continuous time series of 72000 s (20 h) and also 20000 s (5 h and 33 min) each of HR and HP data during the awake and sleep conditions. All subjects had at least 20 h of artefact-free data and thus we used only 72000 s of data for the entire time series. Awake and sleep data (20000 s) were available for all subjects. These HR and HP time series, sampled at 2 Hz, were used to perform spectral analysis and to calculate FD values. Thus spectral analysis was performed on the entire 72000-s and 20000-s time series and the same time series were used to estimate the FDs. APEN values were
obtained only for the 20 000-s time series as these analyses take a long time even on a Pentium-chip-based PC. Figure 1 shows the time series of HR of a female subject with the sleep and awake periods of data used for analyses.

The data were then detrended using a linear detrending technique to calculate the slope and intercept for the linear trend before the computation of spectral analyses. This procedure was performed for the entire 72000 and 20000 s of time series.

Analyses of FD and APEN were performed on both detrended and non-detrended time series of HR and HP.

**Spectral analysis**

The power spectrum was obtained as the magnitude squared of the Fourier transform using a rectangular data window. The powers were integrated in the following frequency bands: ultra low frequency, < 0.0033 Hz; VLF, 0.0033–0.04 Hz; LF, 0.04–0.15 Hz; HF, 0.15–0.5 Hz.

**Fractal dimension**

We used the method described by Katz [24] to compute FD.

The FD of a planar curve is defined as follows:

\[ FD = \frac{\log(L)}{\log(d)} \]

where ‘L’ is the total length of the curve and ‘d’ is the diameter (planar extent) of the curve, which is the furthest distance between the starting point and any other point of the wave form. As suggested by Katz, we adopted the formula:

\[ FD = \frac{\log(L/a)}{\log(d/a)} = \frac{\log(n)}{[\log(n) + \log(d/L)]} \]

where ‘n’ = L/a, which is the total number of steps in the curve (total number of points – 1), and ‘a’ the average distance between successive points. We followed the same method of computation suggested by Katz [24], using a customized software program as in our previous study [25]. We calculated FDs for awake and sleep periods (20 000 s) of HR and HP for all the subjects.

**Approximate entropy**

We used the same technique as in our previous report [25], originally described by Pincus et al. [21], to calculate APEN.

We used a value of 2 for the run length and 2 as the filter value for the HR time series and 20 for the HP time series (approximately 0.2 times the S.D. of the time series).

**Log transformation of data before performing FD and APEN analyses**

We used natural logarithmic transformation of HR and HP time series before the computation of FDs. The filter value for both ln(HR) and ln(HP) used in the analyses
was 0.04 as it is the S.D. (about 0.2) times 0.2 of the time series. The analyses of APEN are not presented on log-transformed data, as the values of APEN obtained were consistently 0.0 even with 10-decimal digit precision.

Statistical analysis
We used BMDP statistical software (Berkeley, CA, U.S.A.) for the analyses. We performed two-tailed paired $t$-tests to compare FDs, APENs and spectral data of awake and sleep HR and HP time series. Significance was assumed at $P \leq 0.05$. We transformed the spectral powers using natural logarithms to normalize the distributions. We used Pearson’s product moment correlations to examine the relationship between mean HR and HP and corresponding FDs and APENs and values of APENs for detrended versus non-detrended data.

RESULTS
Table 1 shows the FD, APEN and spectral analyses of HR and HP for the detrended data for awake and sleep periods. During sleep there was no significant decrease in HR FD but there was a significant increase in HP FD. While there was a significant decrease of APEN for HR from awake to sleep condition, there was a significant increase for HP APEN during sleep.

Spectral data
For the analyses of absolute values of HR, the powers in all frequency bands except HF were significantly decreased during sleep. In contrast, there was no significant decrease of ultra-low-frequency power of HP during sleep. More importantly, for VLF, LF and HF powers, the changes in HP are in the opposite direction to those of HR (Table 1).

Correlations between mean HR, HP, FD and APEN for awake and sleep periods
Although there was a significant correlation between the mean HP and awake FD and awake and sleep APEN (FD: awake, $r = 0.50$, $P = 0.01$; sleep, $r = 0.37$, $P = 0.08$; APEN: awake, $r = 0.61$, $P = 0.001$; sleep, $r = 0.53$, $P = 0.007$), there was no such correlation between mean HR and awake and sleep HR FD ($r = 0.18$ and 0.13 respectively). However, mean HR correlated significantly with mean APEN of awake period ($r = 0.40$, $P = 0.05$) but not that of the sleep period ($r = 0.06$).

Correlations between awake and sleep FD and APEN
There were significant correlations between FD and APEN for both awake (HR: $r = 0.82$; HP: $r = 0.98$, $P = 0.00001$) and sleep conditions (HR: $r = 0.88$; HP: $r = 0.97$, $P = 0.00001$).

Correlations between HF power and FD and APEN
There were significant correlations between HF spectral power of HR and FD and APEN of HR for awake (FD: $r = 0.85$; APEN: $r = 0.87$, $P = 0.00001$) and sleep (FD: $r = 0.86$; APEN: $r = 0.82$, $P = 0.00001$) periods.

There were also significant correlations between HF spectral power of HP and FD and APEN of HP for awake (FD: $r = 0.85$ and APEN: $r = 0.87$; $P = 0.00001$)

![Figure 2](image_url)  
**Figure 2**  
FD values of a straight line and 250, 1000 and 2500 s of instantaneous time series of HR  
As the length of the time series increases the FD values decrease, although there is a higher degree of complexity of the time series in the 2500-s segment.
and sleep (FD: $r = 0.95$ and APEN: $r = 0.90$; $P = 0.00001$) periods.

Linear detrending had no effect at all on the estimation of FDs (72000-s data sets: non-detrended, $1.05 \pm 0.02$ and $1.30 \pm 0.05$ (HR and HP respectively); detrended, $1.05 \pm 0.02$ and $1.30 \pm 0.05$). Results were also similar for sleep and awake periods. For APEN also, there were no significant differences between detrended and non-detrended time series for HR (awake: $0.437 \pm 0.142$ versus $0.437 \pm 0.141$; sleep: $0.374 \pm 0.151$ versus $0.371 \pm 0.146$) or HP (awake: $0.608 \pm 0.204$ versus $0.610 \pm 0.207$; sleep: $0.774 \pm 0.208$ versus $0.787 \pm 0.208$). The correlations between detrended and non-detrended APEN values ranged from 0.96 to 1.0.

**In-Transformed data**

In transformation resulted in identical values of FD for both HR and HP time series for the awake and sleep conditions (awake: $1.000027 \pm 0.000021$; sleep: $1.000035 \pm 1.000044$). There was also no significant difference between awake and sleep periods for the In-transformed time series.

Figures 2 and 3 show the values of FD for different lengths of time series of HR, time series of HP and ln-transformed time series of HR and HP.

**DISCUSSION**

The new findings in this study are that even for measures such as FD and APEN, there can be significant differences between the time series of HR and HP. While there was a significant increase of FD and APEN of HP during sleep, there was no such change for HR time series. In fact, the mean APEN of HR significantly decreased from awake to sleep. Mean HP correlated better with FDs and APENs of HP. Thus FD and APEN analyses using HP need to take mean HP into account when interpreting the results. This is especially important when comparing two populations with significantly different mean HPs. The findings of this study emphasize the need to interpret physiological changes in the HR or HP variability depending on the measure used. Thus one cannot assume that HR and HP can be used interchangeably to analyse these types of data. Although there is nothing sacred about using either measure, one should realize the differences in the analyses when employing HR and HP even for measures such as FD.

Figure 2 shows that the FD decreases as the length of the time series increases, which is related to this method of computation. As we mentioned previously [25], increasing the sampling rate, which increases the length of the segment, also decreases the values of APEN. The values of HR FD in our previous report [25] are considerably higher than the values in this study (about 1.2 for the 256-s segment sampled at 4 Hz compared with 1.05 for the 20000-s segment sampled at 2 Hz). Thus it is important to compare data segments at similar sampling rates and of similar duration.

The FD of a straight line is 1 and it approaches 2 for highly convoluted signals [24]. In this study, the values of FD for the 20000-s segments are about 1.05 for HR and 1.35 for HP. Thus it appears that the unit of measure may be very important because this changes the dispersion of
the data points leading to higher values for HP, lower values for HR and still lower values for the log-transformed HR and HP (Figure 3). However, it is important to note that ln-transformation of HR and HP yielded identical values of FD.

While FD is a relatively simple procedure and is easy to understand, APEN is more complex. The values of APEN also change according to the filter level used. This parameter depends on the S.D. of the data segment. Thus whereas a value of 2 may be appropriate for HR (beats/min) (0.2 times the S.D. for the 20000-s segments in this study), a value of 20 should be used for the HP (ms) series. From a practical point of view, it is also important that the FD computation of a 20000-s (40000 data points) time series takes a few seconds while APEN for the same length of time series takes about 20 min on a 266-MHz Pentium computer. Although there was a very significant correlation between FD values and APEN values for 256-s segments in our previous report ($r = 0.99$) [25], for longer data segments in this study the $r'$ values are in the range of 0.8 to 0.9.

Castiglioni [16] analysed data in different experimental settings and showed that there are substantive differences in the spectra of HR versus HP and that the differences disappear after logarithmic transformation of the time series. The author also suggests that the log-transformed signals have no sign limitations, although HR and HP are both positive, and that this could be a useful property when statistical tests based on normal distributions have to be applied. Bernston et al. [19] suggest that HP has several advantages based on transfer functions relating autonomic nerve traffic to the chronotropic state, which are almost linear when chronotropic effects are expressed in terms of HP. They also suggest that HR can introduce non-linear relationships into these aspects and thus it may be useful to confirm results using both metrics in some instances. It is important to note that after logarithmic transformation, our FD values were identical for HR and HP. This is in agreement with the findings of Castiglioni [16] on spectral data. It should also be noted that log transformation of the time series might not be appropriate for the calculation of APEN as described above.

In this study, we also found significant differences between HR and HP for the changes in spectral absolute powers from awake to sleep period, for all frequency bands. This may not be a problem when relative powers are used. However, Taylor and Lipsitz [17] also caution the use of normalized units as quantitative markers of cardiac autonomic function as these procedures may exaggerate or even reverse changes demonstrated by absolute values of variability. Our findings are similar to those reported by Sapoznikov and Luria [15], who reported on the differences of HR versus HP variability in 109 healthy subjects using 24-h Holter records of ECG. They reported that the high-frequency powers showed greater changes between day and night values when HP was used as the metric compared with HR.

The precise mechanisms underlying ultra-low and very-low-frequency variability are yet to be clarified. However, there is some evidence to suggest that the renin–angiotensin system influences the ultra-low-frequency power [26]. The HF power is influenced by cardiac vagal function which is related to respiratory sinus arrhythmia [3, 27]. The change from supine to standing posture usually causes a decrease in HF power and an increase in LF power due to vagal withdrawal and a relative increase in sympathetic function [28, 29]. However, for comparison of sleep and awake conditions, there is an increase in absolute HF power only for the spectral, FD and APEN analyses of HP, and not for HR, and also not for the FDs of log-transformed series of HR or HP. Thus the interpretation of the results very much depends on the metric used.

In this study, we did not find that linear detrending affected the FD or APEN values of the time series as the HF power mainly contributed to the FD [30]. The significant increase in FD and APEN of HP during sleep is also explained by parallel changes in HF power of HP during sleep. As linear detrending affects mainly the lower frequencies and as the values of FD and APEN correlate significantly with HF power, FD and APEN values were not affected by the detrending procedure. There is a high degree of correlation between the APEN values of both detrended and non-detrended data, and the values are very similar. The mean HP correlated better with FD and APEN of HP than did the corresponding HR measures. Future studies should take into account the above differences between HR and HP in the interpretation of the results, even for measures such as FD and APEN.

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REFERENCES


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