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Review Article

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Effects of Head-Up Tilt on Nonlinear Properties of Heart Rate Variability in Young and Elderly Subjects

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Abstract

In the present study, our aim is to investigate whether responses to the head-up tilt (HUT) on nonlinear properties of heart rate variability (HRV) in young and elderly subjects are different or not. Thirteen young-healthy subjects (24.5 ± 3.7 years) and 18 old-aged healthy subjects (74.5 ± 7.4 years) participated in this study. An electrocardiogram (ECG) in the supine posture, at 0°, and in the standing posture, at 70° of head-up tilt, was recorded. Detrended fluctuation analysis (DFA) and approximate entropy (ApEn), measures of short-/long-term correlation properties and overall complexity of heart rate (HR) respectively, along with spectral components of HR variability (HRV) were analyzed for both the supine and HUT postures. We observed that the short-term fractal exponent α_1 increased during HUT posture ($F(1, 29) = 39.79$, $P = 0.000$), especially, the young subjects showed a significantly higher values compared to the elderly subjects. ApEn significantly decreased ($F(1, 29) = 8.61$, $P = 0.006$) during HUT posture. HUT posture decreased the complexity in HR dynamics and increased short-term fractal exponent values in young subjects but not in elderly subjects. These results imply that there are differences of response to HUT on nonlinear properties between young and elderly subjects.

Keywords: Heart rate variability, Head-up tilt, Age, Nonlinear properties.

Introduction

In cardiology, heart rate variability (HRV) is the most commonly used noninvasive methods to evaluate autonomic regulation of heart rate and conditions of a human heart. The head-up tilt (HUT) test is a standardized physiological stimulus used to investigate the neurocardiogenic condition, and addresses the ability of the cardiovascular circulation to deal with a sudden change in posture. Several studies have reported changes in the linear spectral characteristics of HRV caused by HUT.[1-3] During HUT test, the heart rate (HR) increases and the high-frequency (HF) power of RR intervals decreased as evidence of withdrawal of vagal activity.[2] The normalized low-frequency (nLF) component of HRV increases during tilting, which suggests an increase in sympathetic outflow.[2,3]

Since nonlinear properties are involved in the genesis of human HR fluctuation,[4-6] the nonlinear measures of complexity have been used to probe features in HR behavior.[7] The complexity of the human physiological system, which is reduced in bad health but increased in good health,[8-10] can be analyzed quantitatively by various nonlinear methods. In addition, the HRV exhibits nonlinear dynamic characteristics, such as randomness and aperiodicity,[11-13] and the nonlinearity of HRV decreases in patients with fatal arrhythmia.[13] In the HUT test, the nonlinear analysis of HRV produces a

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different result between patients with essential hypertension and normal subjects.[14]

The aging of a human organism has been in the focus of attention over the past years. One of the most significant systems of vital activity of a human body is its cardiovascular system, so there are many studies on the biological aging of the cardiovascular human system. At rest, elderly subjects show increased sympathetic and decreased parasympathetic activity.[15-17] According to the research on age dependency of cardiovascular autonomic responses to HUT, the HUT-induced increase in HR was more pronounced in the younger subjects, whereas the increase in peripheral resistance was predominantly observed in the older subjects.[15] The HUT test reveals that the dynamic capacity of cardiac autonomic regulation decreases as the age increases in healthy subjects.[15]

Although previous studies have reported the responses to HUT, there is less understanding about the effects of HUT on the nonlinear properties of HRV in young and elderly subjects. In other words, considering the impact of age on the cardiovascular autonomic activity including the nonlinear properties, the different responses to HUT of nonlinear properties in young and elderly subjects will be expected. Therefore, our aim is to investigate whether responses to the HUT in young and elderly subjects, especially in nonlinear properties of HRV, are different or not. To achieve this aim, we recorded the electrocardiogram (ECG) signals for young and elderly subjects during HUT test, and then used linear and nonlinear measures such as the fractal scaling exponents by detrended fluctuation analysis (DFA) and approximate entropy (ApEn) to compare the nonlinear properties of HRV in elderly subjects with those in young subjects.

Materials and methods

Subjects

The volunteers we recruited were aged 20 to 30 years for the young subjects and 60 to 90 years for the elderly subjects. They were informed of the aim and the protocol of the study, and gave their written consent. Originally, 20 young subjects and 50 elderly subjects participated, but we excluded 7 young subjects and 32 elderly subjects from the HRV analysis because they were smokers, took medication and caffeine, or had clinical problems. We therefore ended up with 13 young subjects (age: 24.5 ± 3.7 years; 6 males, 7 females) and 18 elderly subjects (age: 74.6 ± 7.4 years; 9 males, 9 females). None of the subjects had taken any medication for at least one week before this experiment. All of the participants were requested not to drink caffeinated beverages for up to 12 hours before this experiment. Table 1 shows the clinical characteristics of the subjects.

Table 1. Age, gender, and body mass index of the study population

	Young	Elderly
n	13	18
Age (years)	24.5 ± 3.7	74.6 ± 7.4
Male/Female	6 / 7	9 / 9
Body mass index (kg/m²)	20.3 ± 2.3	23.7 ± 3.4

Values are means ± standard deviation

Study protocol

We started the experiment at least 2 hours after the participants' last meal, between 9:30 a.m. and 11:30 a.m., in a quiet, dimly lit room (with a temperature of 23 ± 1℃). After entering the experimental room, which was shielded from electromagnetic waves, each participant laid on the HUT test table in a supine posture (0° from the horizontal line). We instructed each participant about the experimental procedure, and attached the electrodes for the ECG according to the lead II method. We used an electrocardiograph (Biopac MP-100 system, USA) to record the ECG signal. After finishing up the measurement preparation and adaptation period, we started to record ECG signals continuously during the experiment. During recording the signals, we asked the subjects to keep awake.

Participants were maintained in a supine posture in the tilt table for 10 min (baseline recordings), after then the tilt table was inclined to 70° head-up within 1 min and maintained the tilt state for 10 min (HUT posture recording), finally the tilt table returned back to the horizontal line to prepare next experiment. Fig. 1

presents the whole experiment procedure, and Fig. 2 shows the supine posture (left in Fig. 2) and the head-up tilt posture (right in Fig. 2).

Step1	Step2	Step3	Step4	Step5
Measurement Preparation	Adaptation period	ECG recording	Tilting	ECG recording
Procedure →				
Instruction for the experiment	5 min	Supine posture (10 min)	within 1 min	HUT posture (10 min)

Figure 1. Schematic diagram of experimental procedure.

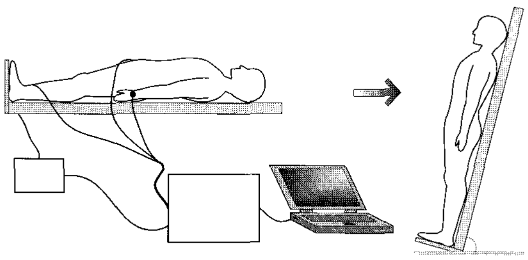


Figure 2. Supine posture (left) and Head-up tilt posture (right).

In this electrocardiograph, the measured analog signal was converted to a digital signal with a sampling frequency of 500 Hz and a resolution of 4.88 μV/LSB. We extracted the R-peaks from the ECG recordings based on Thomkin's algorithm.[18] RR interval data was analyzed during a 5-min baseline period just before head-up tilt when subjects rested supine and during a 5-min period just after HUT when subjects were tilted to 70°. We edited all RR intervals in order to exclude all ectopic beats or artifacts, and RR intervals time series were resampled at a rate of 4 Hz to obtain power spectral density.

Linear spectral analysis

After calculating the mean HR (beat/min) from the ECG signal, we used fast Fourier transformation to obtain the power spectrum of the RR intervals. We then defined the various areas of spectral peaks as follows: the total power (TP), 0 Hz to 0.4 Hz; very low frequency (VLF) power, 0 Hz to 0.04 Hz; low frequency (LF) power, 0.04 Hz to 0.15 Hz; and high frequency (HF) power, 0.15 Hz to 0.4 Hz. The TP, which is a useful tool for detecting abnormal autonomic activity, is larger in normal subjects than in patients with autonomic dysfunction.[19] Furthermore, the LF power mainly provides a measure of sympathetic activity with some influence from the parasympathetic nervous system, whereas the HF power is responsible solely to the parasympathetic nervous system. A logarithmic transformation to the natural base was performed on all spectral components of HRV. We used the normalized LF (nLF = 100 x LF/(TP-VLF)) as an index of sympathetic modulation, the normalized HF (nHF = 100 x HF/(TP-VLF)) as an index of vagal modulation, and the LF to HF ratio (LF/HF) as an index of sympathovagal balance. The spectral component values such as nLF, nHF are presented in normalized units (nu).

Detrended fluctuation analysis (DFA)

Artificial DFA quantifies fractal-like correlation properties by calculating the scaling property of the root-mean-square fluctuation of the integrated and detrended time series data.[20] Briefly, the RR interval data (of total length N) is first integrated, $y(k)=\sum_{i=1}^{k}[u(k)-\bar{u}]$, where $u(k)$ is the ith RR interval and $\bar{u}$ is the average RR interval. Next, the integrated RR interval data is divided into boxed of equal length, n. In each box of length n, a least-squares line is fitted to the data $y(k)$. Next, the integrated data are detrended by subtracting the local trend $y_n(k)$ in each box. The root-mean-square fluctuation of this integrated and detrended time series is calculated by $F(n)=\sqrt{\frac{1}{N}\sum_{k=1}^{N}[y(k)-y_n(k)]^2}$

This computation is repeated over all time scale or box sizes to provide a relationship between F(n), the average fluctuation as a function of box size and the box size n. Typically, F(n) will increase with box size n, thus the slope of the line relating log F(n) to log n is defined as the scale exponent α. A lager value of the scale exponent α represents a smaller fractal dimension and

Tilting
Driver

ECG signal

α=1 corresponds to 1/f noise.[20,21] Based on earlier studies[20,22], we considered computing the exponent α separately for short-term (< 11 beats) and intermediate-term (> 11 beats) scales, yielding the scaling exponents α_1 and α_2, respectively.

Approximate entropy (ApEn)

ApEn quantifies the regularity of time series, so is also called a "regularity statistic". It is represented as a simple index for the overall complexity and predictability of each time series. In our study, ApEn quantifies the regularity of the RR interval. The more regular and predictable the RR interval series, the lower will be the value of ApEn.[7]

First of all, we reconstructed the RR interval time series in the n-dimensional phase space using Takens theorem.[23] Takens suggested the following time delay method for the reconstruction of the state space:

$$D_t = [RR(t),\ RR(t+\tau),\ \ldots, RR(t+(n-1)\tau)]$$

, where n is the embedding dimension and τ is the time delay. In this study, the optimal value of τ was 10. The mean of the fraction of patterns with length m that resemble the pattern with the same length beginnings at interval i is defined by

$$\Phi^m(r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1}\ln\left[\frac{number\ \ of\ |D_m(j)-D_m(i)|<r}{N-m-1}\right].$$

In the above equation, $D_m(i)$ and $D_m(j)$ are state vectors in the embedding dimension, m. Given N data points, we can define ApEn as,

$$\mathrm{ApEn}(m,r,N)=\Phi^m(r)-\Phi^{m+1}(r)$$

, where ApEn estimates the logarithmic likelihood that the next intervals after each of the patterns will differ. In general, the embedding dimension, m, and the tolerance, r are fixed at m = 2 and $r = 0.2 \times SD$ in physiological time series data.[24,25]

Statistical analysis

For all our analyses, we used SPSS (version 12.0) and represented the data in the form of a mean ± standard error of means (SEM). We used analyses of variance (ANOVA) for repeated measurements with supine versus HUT as repeated measures and young versus elderly subjects as grouping factor. Significant effects were followed up by paired t-test to compare young and elderly subjects for supine and HUT separately. Any P value less than 0.05 was accepted as significant.

Results

We observed no syncopal or presyncopal symptoms in any subjects during the tilting. In addition, the HR, sex distribution and body mass index were not significantly different between the two groups, and there was no significant gender difference in HRV values during HUT. The tilting had a major effect on the linear and nonlinear HRV parameters for both groups.

Table 2. Linear and nonlinear measures of heart rate variability in young and elderly subjects for both the supine and the HUT posture (Mean ± SEM)

	Young		Elderly	
	Supine	Tilting	Supine	Tilting
TP (ln)	7.55 ± 0.19	7.18 ± 0.17 ^{c}	5.98 ± 0.24	5.98 ± 0.18 ^{c}
LF power (ln)	6.17 ± 0.23	6.14 ± 0.22 ^{c}	4.10 ± 0.25	4.08 ± 0.19 ^{c}
nLF power (nu)	39.50 ± 5.05	68.26 ± 5.88 ***	+ 42.04 ± 3.96	57.71 ± 4.21 ††
HF power (ln)	6.65 ± 0.23	5.21 ± 0.28 ^{***c}	4.45 ± 0.28	3.73 ± 0.26 $^{\dagger c}$
nHF power (nu)	60.50 ± 5.05	31.74 ± 5.88 ***	57.96 ± 3.96	42.29 ± 4.21 ††
LF/HF	0.87 ± 0.23	4.11 ± 1.19 **	0.91 ± 0.17	1.98 ± 0.44 †
ApEn	1.11 ± 0.03	1.05 ± 0.04	1.10 ± 0.02	0.92 ± 0.05 ††
α1	0.93 ± 0.06	1.47 ± 0.09 ^{***a}	0.97 ± 0.05	1.13 ± 0.07 ^{a}
α2	0.72 ± 0.06	0.81 ± 0.05	0.81 ± 0.04	0.92 ± 0.05

TP = total power; LF = low frequency; HF = high frequency; LF/HF = low/high frequency power ratio; nLF = normalized low frequency; nHF = normalized high frequency; ApEn = approximate entropy; α1 = short-term fractal scaling exponent; α2 = long-term fractal scaling exponent.

** P < 0.01, *** P < 0.001 : baseline vs. tilting within young subjects;

† P < 0.05, †† P < 0.01 : baseline vs. tilting within elderly subjects;

[a] $P < 0.05$, [c] $P < 0.001$: young subjects vs. elderly subjects.

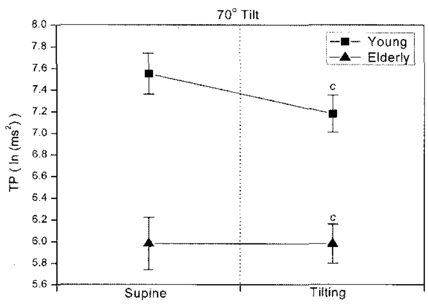
Table 2 shows the mean values and SEM of the TP, LF power, nLF power, HF power, nHF power, LF/HF, ApEn, α_1 and α_2 for the young and elderly subjects before and during HUT.

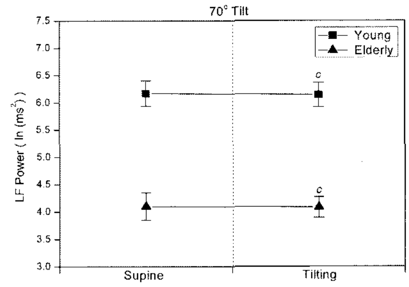
Effects of HUT on linear spectral properties

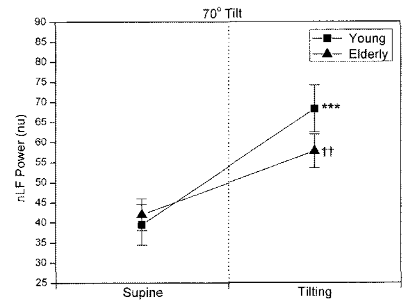
There were no significant changes in TP, LF power between supine and HUT. However, there were significant differences in the TP ($F(1, 29) = 38.37$, $P = 0.000$) and LF power ($F(1, 29) = 70.97$, $P = 0.000$) between young and elderly subjects. In this case, the elderly subjects presented significantly lower values than those of young subjects for both TP and LF power.

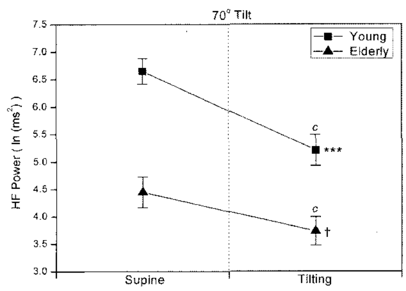
When we compared the results of the HUT posture with those of the supine posture, we observed a significant increase in the nLF ($F(1, 29) = 30.88$, $P = 0.000$) power and a significant decrease in the nHF ($F(1, 29) = 30.88$, $P = 0.000$) power during HUT posture, both in young subjects and elderly subjects.

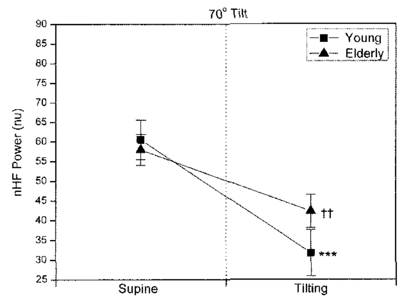
HF power ($F(1, 29) = 28.53$, $P = 0.000$) was significantly decreased and LF/HF ($F(1, 29) = 16.91$, $P = 0.000$) was significantly increased during HUT posture. In the case of the HF power, the elderly subjects presented significantly lower values than those of young subjects. In addition, there was a significant interaction effect on posture and group in LF/HF ($F(1, 29) = 4.28$, $P = 0.048$). In addition, there weren't any significant differences between young and elderly subjects and interaction effects in the nLF power, nHF power and HF. Fig. 3 presents the influence of HUT on linear spectral measures such as TP, LF power, HF power, nLF power, nHF power, and LF/HF.











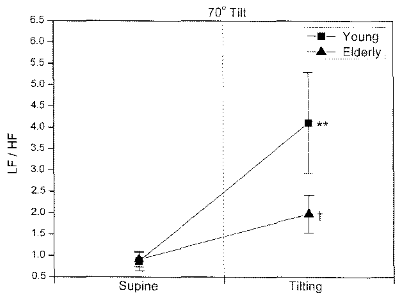


Figure 3. The influence of HUT on linear measures of HRV in young subjects (■, n = 13) and elderly subjects (▲, n = 18). Values are means ± SEM.
TP = total power; LF = low frequency; HF = high frequency; LF/HF = low/high frequency power ratio; nLF = normalized low frequency; nHF = normalized high frequency.
** P < 0.01, *** P < 0.001 : baseline vs. tilting within young subjects;
† P < 0.05, †† P < 0.01 : baseline vs. tilting within elderly subjects;
^{c} P < 0.001 : young subjects vs. elderly subjects.

Effects of HUT on nonlinear properties

ApEn significantly decreased during HUT posture ($F(1, 29) = 8.61$, $P = 0.006$), but there were no interaction effect and between group effect. There weren't any significant changes in α_2, thus, HUT did not alter long-term fractal scaling exponent.

However, there were significant changes in α_1. The short-term fractal scaling exponent α_1 significantly increased during HUT posture ($F(1, 29) = 39.79$, $P = 0.000$), especially, the young subjects showed a significant increase during HUT posture in α_1 ($P < 0.01$).

In addition, α_1 differed significantly between young and elderly subjects ($F(1, 29) = 4.84$, $P = 0.036$), and there was a significant interaction effect ($F(1, 29) = 13.36$, $P = 0.001$) on posture and group. According to the post-hoc analysis, this interaction effect resulted from a significant increase within young subjects and difference between young and elderly subjects. Thus, these results for α_1 mean that HUT was associated with an increase in the short-term fractal scaling exponent and the young subjects represented higher short-term fractal scaling exponent values compared to that of the elderly subjects. Fig. 4 represents the influence of HUT on nonlinear measures such as ApEn, α_1, and α_2.

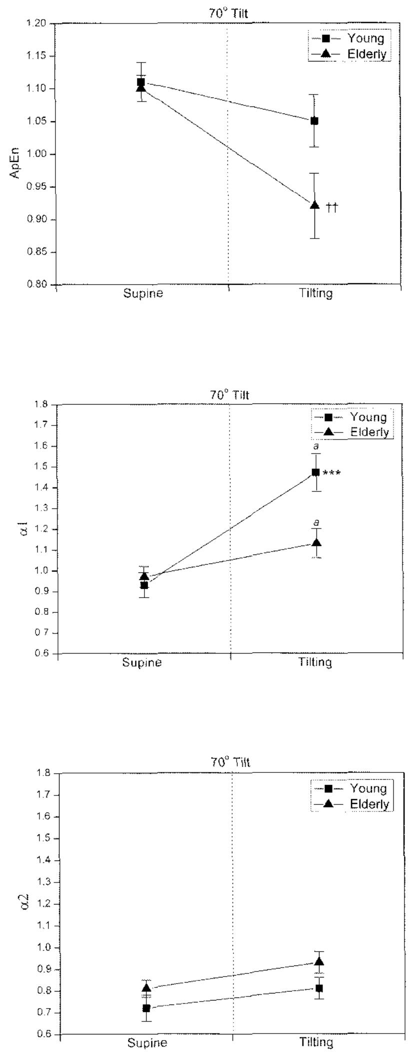


Figure 4. The influence of HUT on nonlinear measures of HRV in young subjects (■, n = 13) and elderly subjects (▲, n = 18). Values are means ± SEM.
ApEn = approximate entropy; $\alpha 1$ = short-term fractal scaling exponent; $\alpha 2$ = long-term fractal scaling exponent.
*** P < 0.001 : baseline vs. tilting within young subjects;
††P < 0.01 : baseline vs. tilting within elderly subjects;
^{a} P < 0.05 : young subjects vs. elderly subjects.

Discussion

The main finding of this study is that there are differences of responses to HUT on nonlinear properties between young and elderly subjects. Especially, the short-term fractal scaling exponent α_1 significantly increased during HUT posture in young subjects but not in elderly subjects. However, the HUT does not change the long-term fractal scaling exponent α_2.

The DFA technique is a modified root-mean-square analysis of a random walk, and it quantifies the presence or absence of the short-term and long-term fractal correlation properties in RR time series. In this method, a fractal-like signal results in an empirical value of ~ 1.0, a random signal results in a value of 0.5, and a strongly correlated signal behavior results in an empirical value of 1.5.[20] Increased short-term fractal exponent values observed during the HUT in the present study imply stronger correlation properties of short-term HR dynamics during HUT interventions compared with the supine resting condition. In addition, these results showed that HUT result in a change in the HR dynamics from a normal fractal-like dynamics toward an increase in the short-term correlation properties of HR dynamics only in young subjects.

On the other hand, overall complexity ApEn significantly decreased during HUT posture. This result is in accordance with the previous study.[26] ApEn is the rate of information production, which is the key to the measurement of irregularity, [24,27,28] and is basically designed to measure the regularity and complexity of time series data. Lower ApEn values indicate a more regular (less complex) signal, higher values indicate more irregular (greater complexity).[24] The present data showed that complexity in HR dynamics decreased during HUT.

Examining the potential for nonlinear chaos in dynamic events often allows us to uncover the mathematical form of physiological mechanisms, and sometimes to predict how their functioning depends on the relevant parameters.[29] Chaotic parameters have been found to decrease after autonomic blockade induced by propranolol and atropine, [30] during exercise[31] and with aging.[8] The correlation dimension and Lyapunov exponents were reported to be low in patients with a neural connection disorder between the heart and the central nervous system, such as heart transplant patients.[32] There is a reason why we used DFA and ApEn among many nonlinear measures applicable to investigate the HR dynamics in response to HUT for young and elderly subjects. In general, nonlinear analytical methods need many data points compared to conventional linear methods.[20,33] Even though the nonlinear properties are involved in the genesis of human HR fluctuation, only a limited number of HR data can be obtained during HUT. The need of many data points might be one reason why only a few studies had applied nonlinear methods to the analysis of HR dynamics during HUT.[26] DFA and ApEn may overcome this problem[20,24] because these methods are applicable to relatively limited time series.[26] In addition, DFA seems to be suitable for analysis of non-stationary time series.[20]

The interplay between the sympathetic and vagal regulation of HR is usually organized in a reciprocal fashion, i.e., increased activity in one system is accompanied by decreased activity in another.[2,34] In the present study, the LF/HF increased in all subjects in response to tilting, which is in agreement with previous studies.[14,32,35] In addition, the present study shows that aging is associated with changes in the autonomic regulation during HUT. The normalized HF power decreased and the normalized LF power increased as evidence of withdrawal of vagal activity and enhanced sympathetic outflow during HUT.[7] Changes in autonomic regulation caused by HUT also resulted in concordant changes in the short-term fractal properties of HR dynamics.

A limitation in our study is that we did not evaluate healthy states by clinical statements, and did not assess other clinical variables such as circulatory, heart and arterial characteristics. Further experimental work will be needed to complement these defects.

References

1. Fei L, Anderson MH, Statters DJ, Malik M, Camm AJ. Effects of passive tilt and submaximal exercise on spectral heart rate variability in ventricular fibrillation patients without significant structural heart rate disease. Am Heart J. 1995;129:285-290.
2. Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power spectrum analysis of heart rate variability to assess the changes in sympathvogal balance during graded orthostatic tilt. Circulation 1994;90:1826-1831.
3. Radelli A, Bernardi L, Valle F, Leuzzi S, Salvucci F, Pedrotti L, Marchesi E, Finardi G, Sleight P. Cardiovascular autonomic modulation in essential hypertension: effect of tilting. Hypertension 1994;24:556-563.

4. Braun C, Kowallik P, Freking A, Hadeler D, Kniffki KD, Meesmann M. Demonstration of nonlinear components in heart rate variability of healthy person. Am J Physiol Heart Circ Physiol. 1998;275:H1577-H1584.
5. Kanters JK, Hojgaard MV, Agner E, Holstein-Rathlou NH. Short- and long-term variations in nonlinear dynamics of heart rate variability. Cardiovasc Res. 1996;31:400-409.
6. Tulppo MP, Mäkikallio TH, Seppänen T, Airaksinen KEJ, Huikuri HV. Heart rate dynamics during accentuated sympathovagal interaction. Am J Physiol Heart Circ Physiol. 1998;274: H810-H816.
7. Tulppo MP, Hughson RL, Mäkikallio TH, Airaksinen KEJ, Seppänen T, Huikuri HV. Effects of exercise and passive head-up tilt on fractal and complexity properties of heart rate dynamics. Am J Phyisol Heart Circ Physiol. 2001;280: H1081-H1087.
8. Kaplan DT, Furman MI, Pincus SM, Ryan SM, Lipsitz LA. Aging and the complexity of cardiovascular dynamics. Biophys. J. 1991;59:945-949.
9. Signorini MG, Guzzetti S, Manzoni C, Milani S, Cerutti S. Multiparametric analysis of HRV signal by linear and nonlinear methods in heart failure patient population in Proceedings of the 20th Annual International Conference of the IEEE Engineering in Medicine and Biology Society 1998;20:322-325.
10. Wagner CD, Persson PB. Chaos in blood pressure control. Cardiovasc Res. 1996;31: 380-387.
11. Babloyantz A, Destexhe A. Is the normal heart a periodic oscillator? Biol. Cybern. 1998;58:203-211.
12. Elbert T, Ray WJ, Kowalik ZJ, Skinner JE, Graf KE, Birbaumer N. Chaos and physiology: deterministic chaos in excitable cell assemblies. Physiol. Rev. 1994;74:1-47.
13. Goldberger AL, West BJ. Application of nonlinear dynamics to clinical cardiology. Ann. NY Acad. Sci. 1987;504:195-213.
14. Kagiyama S, Tsukashima A, Abe I, Fujishima S, Ohmori S, Onaka U, Ohya Y, Fujii K, Tsuchihashi T, Fujishima M. Chaos and spectral analyses of heart variability during head-up tilting in essential hypertension. J. Autonomic nervous System 1999;76:153-158.
15. Laitinen T, Niskanen L, Geelen G, Länsimies E, Hartikainen J. Age dependency of cardiovascular autonomic responses to head-up tilt in healthy subjects. J Appl Physiol. 2004;96: 2333-2340.
16. Colosimo A, Giuliani A, Mancino AM, Piccirillo G, Marigliano V. Estimating a cardiac age by means of heart rate variability. Am J Physiol Heart Circ Physiol. 1997;273: H1841-H1847.
17. Craft N, Schwartz JB. Effects of age on intrinsic heart rate, heart rate variability, and AV conduction in healthy humans. Am J Physiol Heart Circ Physiol. 1995;268: H1441-H1452.
18. Tompkins WJ. Bimedical digital signal processing. Prentice Hall PTR, Upper Saddle River, New Jersey 07458, 1995.
19. Pumprla J, Howorka K, Groves D, Chester M, Nolan J. Functional assessment of heart rate variability: physiological basis and practical applications. Int. J. Cardio. 2002;84:1-14.
20. Peng C-K, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heart-rate time series. Chaos 1995;5: 82-87.
21. Peng CK, Hausdorff JM, Goldberger AL. Fractal mechanisms in neuronal control: human heartbeat and gait dynamics in healthy and disease. In: Walleczek J, editor. Self-organized biological dynamics and nonlinear control: toward understanding complexity, chaos, and emergent function in living systems. Cambridge (UK): Cambridge University Press; 2000. p. 66-96.
22. Ho KKL, Moody GB, Peng C-K, Mietus JE, Larson MG, Levy D, Goldberger AL. Predicting survival in heart failure case and control subjects by use of fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. Circulation 1997;96; 842-848.
23. Takens F. Detecting strange attractors in turbulence In: Dold A and Eckmann B (Eds) Lecture Notes in Mathematics. Springer, Heidelberg 1981;898:366-381.
24. Pincus SM. Approximating Markov chains. Proc. Natl. Acad. Sci. USA 1992;89:4432-6.
25. Pincus SM, Goldberger AL. Physiological time-series analysis: what does regularity quantify? Am. J. Physiol. 1994;266:H1643-56.
26. Kubo Y, Murakami S, Matsuoka O, Hotta N, Oinuma S, Shinagawa M, Omori K, Nunoda S, Otsuka K, Ohkawa S, Cornélissen G, Halberg F.

Toward chronocardiologic and chronomic insights: dynamics of heart rate associated with head-up tilting. Biomed & Pharmacotherapy 2003;57:110s-115s.

27. Kim JS, Park JE, Seo JD, Lee WR, Kim HS, Noh JI, Kim NS, Yum MK. Decreased entropy of symbolic heart rate dynamics during daily activity as a predictor of positive head-up tilt test in patients with alleged neurocardiogenic syncope. Phys. Med. Biol. 2000;45:3403-3412.
28. Moraru L, Tong S, Malhotra A, Geocardin R, Thakor N, Bezerianos A. Investigation of the effects of ischemic preconditioning on the HRV responses to transient global ischemia using linear and nonlinear methods. Medical Eng. Phy. 2005;27(6):465-473.
29. Bassingthwaighte J., Liebovitch L. S., West B J., 1994. Fractal Physiology. Oxford University.
30. Hagerman I, Berglund M, Lorin M, Nowak J, Sylven C. Chaos-related deterministic regulation of heart rate variability in time and frequency domains: effects of autonomic blockade and exercise. Cardiovasc. Res. 1996;31:410-418.
31. Nakamura Y, Yamanoto Y, Muraoka I. Autonomic control of heart rate during physical exercise and fractal dimension of heart rate variability. J Appl Physiol. 1993;74: 875-881.
32. Guzzetti S, Magatelli R, Borroni E, Mezzetti S. Heart rate variability in chronic heart failure. Autonomic Neuroscience: Basic and Clinical 2001;90: 102-105.
33. Poon C-S, Merrill CK. Decrease of cardiac chaos in congestive heart failure. Nature 1997;389:492-5.
34. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circ. 1991;84:482-492.
35. Huikuri H, Ylitalo A, Pikkujämsä S, Ikäheimo M, Airaksinen K, Rantala A, Lilja M, Kesäniemi Y. Heart rate variability in systemic hypertension. Am J Cardiol. 1996;77: 1073-1077.