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IMPACT OF HYPOXIA ON HEART RATE VARIABILITY BASED ON SAMPLE ENTROPY

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ABSTRACT

In this study, changes in heart rate variability (HRV) induced by exposure to hypoxia were evaluate in healthy male. The sample entropy as a non-linear method of HRV analysis was used; it's a powerful way to analyze biological system. Our aim was to investigate the influence of stepwise hypoxia on HRV using sample entropy, we tested nine healthy yellow males (age=35 $\pm$ 5) at 3600m, 4000m, 4400m, 4800m during rest, these were a part of the acclimation test. An increase in sample entropy at high altitude compared to 1000m was established in this research. The parameters showed similar tendencies during different altitude, but not so obvious. The changing of sample entropy in every day was analyzed. Our results indicate that hypoxia exerts an influence on HRV; it also suggested that acute exposure to normobaric hypoxia induces increases in sympathetic vasomotor activity and cardiac sympathetic dominance resulting in an increased heart rate.

Keywords: *Heart Rate Variability (HRV), Sample Entropy, Hypoxia*

1. INTRODUCTION

Nonlinear dynamic analysis is a useful approach to understanding biological system. Most biological signals are nonlinear and non-stationary time series, such as heart rate variability (HRV). HRV is a non-invasive indicator of cardiac activity; it can be reduced in stressful situations, such as exposure to hypoxia while the heart rate (HR) is increased at the same time [1]. Assessing HRV can also measure autonomic nervous activity; the reliability of this method has already been examined in various studies, including large-scale ischemic heart disease studies [2].

Hypoxia is an important topic in occupational and environmental medicine, exposure to decreased partial pressures of inspired O_2 induces hypoxemia in humans who breathe air containing less than 21% under normobaric conditions. Also, the physiology of hypoxia under hypobaric conditions has become important in aviation and high altitude medicine, since the number of individuals traveling by air or reaching high altitudes has obviously increased [3]. Hypoxemia systematically alters the neurological regulation of cardiovascular factors. Such cardio-vasular neuroregulation can be non-invasively analyzed using spectral analysis of oscillations in heart rate [4].

Fumihiko analyzed the impact of acute hypoxia on heart rate and blood pressure variability in conscious dogs by frequency domain analysis [5], Shigeru did some research on relationship between arterial oxygen saturation and heart rate variability at high altitudes [6], Jason investigated the intermi-ttent hypoxia and respiratory plasticity in humans and other animals, to make sure if exposure to intermittent hypoxia promote or mitigate sleep apnoea [7]. Most of these studies are given by time and frequency domain, as the heart rate variability are not stationary time series, in this paper, sample entropy are used to estimate the impact of hypoxia on heart rate variability. Through this method, more detail about the nonlinear characters of cardiac sympathetic is looking forward to be found.

2. METHOD AND SUBJECTS

2.1 Sample Entropy

Sample entropy was developed by Richman based on approximate entropy; it's a new algorithm to measure the complexity of time sequence [8]. Sample entropy has two important properties. First, it is largely independent on the record length and eliminate self-matches, so, the sample entropy algorithm is simpler than the approximate entropy algorithm, requiring approximately one-half as much time to calculate. Second, sample entropy

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displays relative consistency under circumstances. The meaning of sample entropy is the rate of generation of new information, which can be applied to the typically short and noisy time series of clinical data.

For a time series of N points, u(1),u(2),⋯U (N), sample entropy was proceeding as follows [8]:

(1)forms the N-m+1 vectors $X_m(i)$ for i=1~N-m+1, where $X_m(i)$= [u(i),u(i+1),⋯U (i+m-1)] is the vector of m data points from u (i) to u (i+m-1).

(2)The distance between two such vectors is defined to be d[x(i),x(j)] =max[u(i+k)-u(j+k)], i, j=1~N-m+1,k=1~m-1. It is the maximum difference of their corresponding scalar comp-onents.

(3)Let B_i be the number of vectors $X_m(j)$ within r of $X_m(i)$ and let A_i be the number of vectors $X_{m+1}(j)$ within r of $X_{m+1}(j)$ .Define the function

$$B_i^m(r) = \frac{B_i}{N-m}$$

In calculating $B_i^m(r)$, the vector X_m (i) is called the template, and an instance where a vector X_m (j) is within r of it is called a template match. $B_i^m(r)$ is the probability that any vector X_m (j) is within r of X_m (i).

(4)Calculate the average of the natural logarithms of the functions $B_i^m(r)$

$$B^m(r) = \frac{1}{N-m+1}\sum_{i=1}^{N-m+1} B_i^m(r)$$

(5)Let m change to m+1, repeat the above steps to calculate $B_i^{m+1}(r)$.

(6)Theoretically, the sample entropy of this series is

$$SampEn(m,r) = \lim_{N\to\infty}\left\{-\ln\left[\frac{B^{m+1}(r)}{B^m(r)}\right]\right\}$$

(7)When the length of this time series N is limited, the above formula can be estimated by

$$SampEn(m,r,N) = -\ln\left[\frac{B^{m+1}(r)}{B^m(r)}\right]$$

The value of sample entropy is associate with r and m, so it is very important to determinate the values of these two parameters. For smaller r values, one usually achieves poor conditional probability estimates, while for larger r values, too much detailed system information is lost. To avoid a significant contribution from noise in a sample entropy calculation, one must choose r larger than most of the noise. There is a preliminary conclusion given by Pincus that choices of r ranging from 0.1 to 0.2 SD of the u (i) data would produce reasonable statistical validity [9]. For larger m, too much calculation are given, time will be long. In general, m is 1or 2. In this research, m is 2; r is 0.2 SD of the u (i) data.

2.2 Hypoxia Cabin and Subjects

In this research, hypoxia cabin is designed and built independently. Through control the flow ratio of nitrogen and air, different altitude from 0-8000 meter can be simulated.

Nine healthy yellow males (Table 1) participated in this study. None of the subjects had cardiovascular or pulmonary disease, and none was receiving any medication. All subjects lived at an altitude of around 1000m, and none was acclimatized to above 3500m before the experiment. No subject took any drugs during this period. Written informed consent was obtained from each subject.

Table1. Main Biometrical Characteristics of the subjects

N=9	Age (year)	Height (cm)	Body mass(kg)	HR (No/min)
Mean ± SD	35.6 ± 5	179.3 ± 4.7	86.1 ± 8.9	65 ± 9.8

2.3 Experimental protocol

Subjects completed resting measurement with the upright sitting position in hypoxia cabin throughout a 7-day period. Each training lasted 120 minutes, the simulated altitude were from 3600m, 4000m, 4400m to 4800m, each altitude lasted 30 minutes, as shown in figure 1.

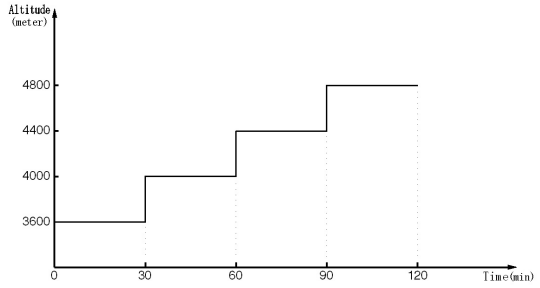

Figure 1. Schematic Diagram of Experiment Protocol

All data were acquired using an analog-to-digital converter interfaced with a computer. Measured R-R intervals were determined from the electrocardiogram, there's a 30 minutes HR data in figure 2.

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HR variability data were sampled at 1000 Hz and stored for subsequent analysis. Arterial oxygen saturation SaO_2 which was monitored using a portable monitor, the SaO_2 probe was set on the right index finger. 、

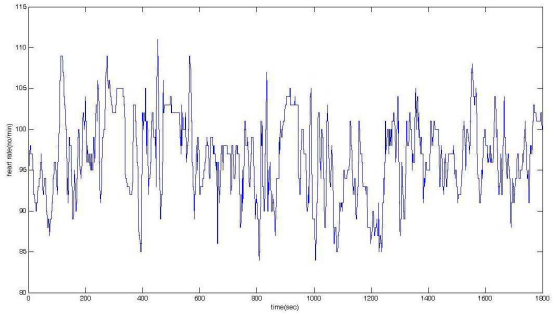


Figure 2. Heart Rate Data of 30 Minutes

2.4 Statistical analysis

The SPSS software for Windows (version 19) was used for computations. The results are expressed as an arithmetic mean and standard deviation. Changes in HRV parameters associated with exposure to a high altitude were evaluated with Student t test. Differences below the confidence limit α =5% were considered statistically significant.

3. RESULT

3.1 Arterial oxygen saturation Analysis

Arterial oxygen saturation SaO_2 at 3600m, 4000m,

4400m and 4800m were lower one by one, as shown in figure 3.

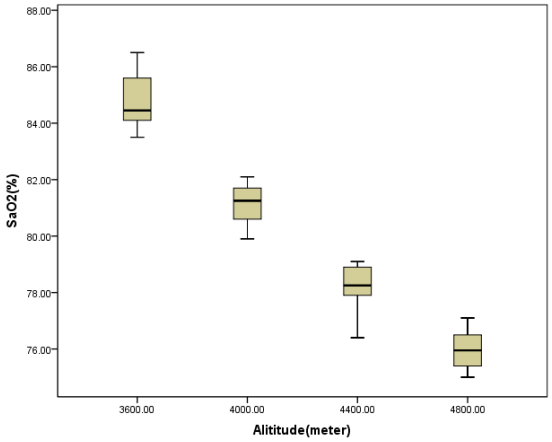


Figure 3. SaO_2 of Different Altitude

3.2 Heart Rate Variability Analysis

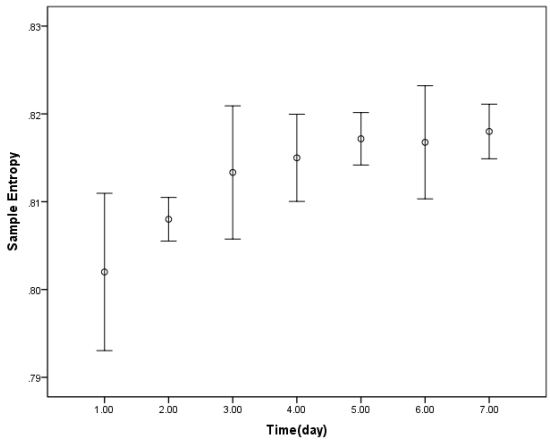
The length of the R-R intervals was regulated and validated before analysis, the sample entropy of heart rate variability to every altitude was calculated using the way expressed in 2.1, the second ten minutes data of every period were used to compute the sample entropy, because the first or the last ten minutes data may be not stability enough.

The Altitude, HR, R-R interval and sample entropy are shown in table 2. All the data in table 2 are the average value of different altitude in the whole seven days. With the altitude higher, heart rate is higher; correspondingly, the R-R interval is shorter. The sample entropy of every altitude differed compared to normoxia, and it was not obviously changed with different high altitude, only a little higher can be observed through them. Our research was only focus on the resting situation; there was mo exercise during the whole experiment.

Table2. HRV Parameter of Different Altitude

Altitude (m)	HR (n/min)	RR interval (ms)	Sample entropy
1000	65 ± 9.8	923 ± 89.4	0.76 ± 0.03
3600	79 ± 7.3	759 ± 92.5	0.81 ± 0.07
4000	83 ± 9.1	722 ± 95.8	0.83 ± 0.08
4400	89 ± 8.7	674 ± 88.3	0.84 ± 0.06
4800	95 ± 9.4	631 ± 97.1	0.85 ± 0.04

The changing of sample entropy in every day was shown in figure 4. The tendency of every altitude was almost similar from 3600m to 4400m. In the first three days, sample entropy was increasing, till the forth day; it arrived to a stability area ultimately. There was some fluc-tuation at the period. To 4800m, the tendency was changed. In the first two days, sample entropy was increasing, till the third day, it was decreased suddenly, then, it began to increase again, this time, and the up tendency did not stop till the senventh day.



(A). Sample Entropy of 3600m

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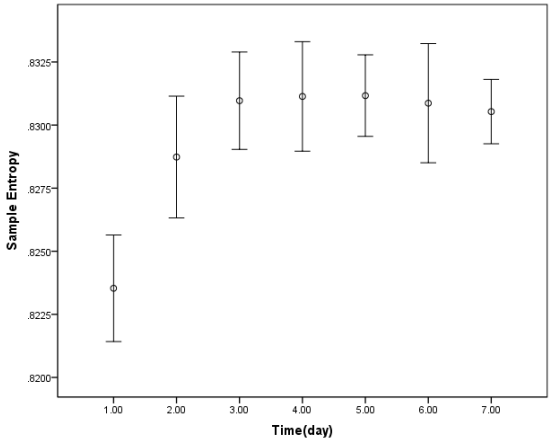
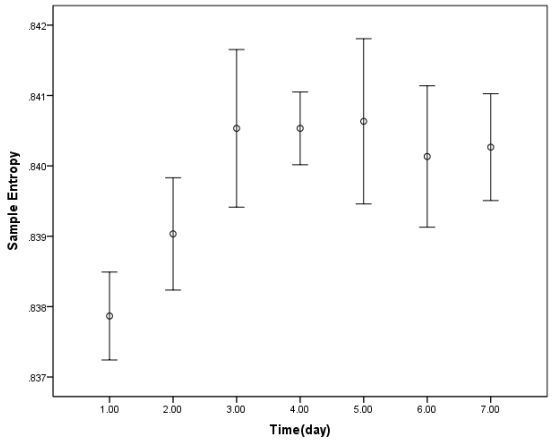
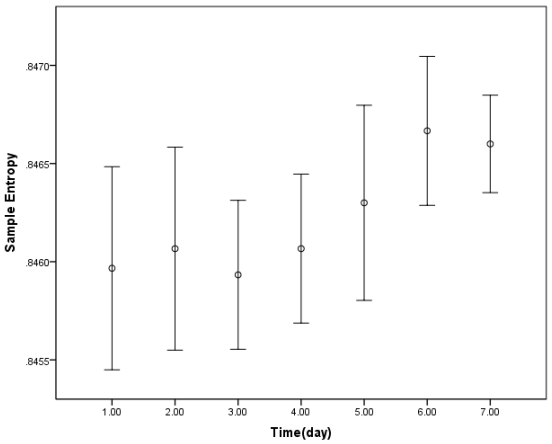


(b). Sample Entropy of 4000m



(c). Sample Entropy of 4400m



(d). Sample Entropy of 4800m

Figure 4. Sample Entropy of Every Day At Each Altitude

4. DISCUSSION AND CONCLUSION

Sample entropy, a nonlinear signal processing approach, was used as a measure of signal complexity to evaluate the behavior of heart rate variability in simulated hypoxia. HRV, this non-invasive and real-time parameter is the beat to beat alteration of the R-R intervals in an electrocardiogram. This method is the most commonly used monitoring of autonomic nervous activities.

The present study displayed two main findings. Acute exposure to normobaric hypoxia changes cardiovascular autonomic nerve modulation and balance, even when hypoxemia is mild. Such hypoxia induced increases in sympathetic vasomotor activity, and sympathetic dominance on the cardiac autonomic nerve activity resulting in an increased heart rate. These modulations were shown through the change of sample entropy. When first exposure to hypoxia, the balance of cardiovascular autonomic nervures system was broken, that was embodied by the increasing of sample entropy at the first days. At the later days, new balance was rebuilt; acclimation changed the vitality of sympathetic nerve and parasympathetic nerve, so the sample entropy only changed in a small area finally.

When going to high altitudes, the human body has to cope with several stressors: hypoxia, cold, exercise, radiation, etc. Undoubtedly, hypoxia is the most important stressor and in certain circumstances, e.g., when going too high too fast, the body is unable to adapt sufficiently and life-threatening illnesses may be the consequences [10]. Therefore, the stepwise in altitude (hypoxia) allows the body to adapt and to prevent those illnesses. [11]

Most studies measured autonomic nervous activity by assessing HRV by time or frequency domain [12, 13]. Power of HRV was quantified by determining the areas of the spectrum in two component widths: LF and HF. High-frequency components are considered to be associated solely with cardiac parasympathetic activity, whereas the low-frequency components are associated with both parasympathetic and sympathetic activity. The LF/HF ratio is an index of cardiac sympathetic tone. The sample entropy approach does not have major improvement over the existing frequency domain methods. In fact, its accuracy is relatively low; its main achievement however, is the simplicity of computation, and the showing of dynamical system components.

In this paper, we used sample entropy to analysis HRV, the results of this study carried out under simulated hypoxia conditions indicate that hypoxia per se affects the functioning of the autonomic nervous system. Further studies are needed to confirm our results, especially to more subjects. Sample entropy and other nonlinear

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methods are useful tools to detect hypoxia acclimation.

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