Heart Rate Variability Analysis During Stepwise Hypoxia from 3000m to 4500m

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Abstract: In this paper, the aim was to investigate the influence of stepwise hypoxia on HRV during rest and exercise states through sample entropy. SampEn is a powerful way to analyze non-linear biological signal, such as HRV. In ten days, 4 healthy yellow males stayed in the hypoxia cabin for 130 min every day. It's divided into four periods: two rest periods of 30 minitues and 60 minutes, two exercise periods of 20 min, the rest and exercise periods were across. Heart rate and SaO_2 signals were collected. The simulated altitude of hypoxia cabin was from 3000m to 4500m meters. The SampEn of every altitude was calculated and compared. Our results indicate a vagal control withdrawal and a sympathetic activity increase under normobaric hypoxia, that's how the intermittent stepwise hypoxic training induce the response of the autonomic nervous system.

[Liu YY, Cao ZT, Yang J, Yu MS, Wang BH, Wan YY, Wang HT. **Heart Rat Variability Analysis During Stepwise Hypoxia from 3000m to 4500m**. *Life Sci J* 2013; 10(3): 1127-1131] (ISSN: 1097-8135). http://www.lifesciencesite.com. 164

Keywords: Heart Rate Variability (HRV), Stepwise Hypoxia, Altitude

1. Introduction

Because of the advance of transport technology, many travelers are able to visit highlands or moderate altitudes without having any special training and acclimatization. This trend has had a significant impact on the trends in alpine accidents (Hackett, 2001). Exposure to decreased partial pressures of O_2 induces hypoxemia in humans who breathe air containing less than 21% under normobaric conditions. Physiologically, the main problem of altitude exposure and hypoxia for the body is the decreased oxygen pressure. The physiology of hypoxia has become important in aviation and high altitude medicine (WHO, 2005).

Hypoxemia can systematically alter the neurological regulation of cardiovascular factors. Such cardiovascular neuroregulation can be non-invasively analyzed by using spectral analysis of oscillations in heart rate (Iwasaki, 2006). Autonomic nervous activity can be measured by assessing heart rate variability (HRV). This method is reliable, various studies has already examined it, including large-scale ischemic heart disease studies (Barron, 1998).

HRV is nonlinear and non-stationary time series, as most biological signals. Sample entropy (SampEn) is one of nonlinear dynamic analysis, is a useful approach to biological system. It's used to calculate and investigate the dynamics of neonatal HRV, the result falls before clinical signs of neonatal sepsis (Douglas, 2002).

Another load which is known to exacerbate acute high altitude mountain sickness is exercise (Buchheit, 2004). Shigeru did some research on relationship between HRV and arterial oxygen saturation at high altitudes (Saito, 2005).

Most of these researches are studied by time and frequency domain, which take the HRV as stationary time series. HRV signal is nonlinear and non-stationary. In this paper, more detail about the nonlinear characters of cardiac sympathetic are tried to be found, as SampEn are used to investigate the HRV during rest and exercise in stepwise hypoxia.

2. Material and Methods

2.1 Sample entropy

Richwman developed SampEn based on approximate entropy, which is a algorithm to measure the complexity of time sequence. The meaning of SampEn is the rate of new information's generation (Joshua, 2000). SampEn eliminate dependent on the record length and self-matches, so it is simpler than the approximate entropy algorithm. This method can be applied to the typically short and noisy time series of clinical data, such as neonatal heart rate (Barron, 1998).

For a time series of N points, u(1),u(2),⋯u(N), SampEn was proceed as follows(Joshua, 2000):

(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 as 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 components.

(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 SampEn 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

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

There are two parameters: r and m. It's important to determinate the values of them. In general, m is 1or 2. Smaller r value usually causes poor conditional probability estimate, larger r values causes losing of detailed system information. In an SampEn calculation, to avoid a significant contribution from noise, one must choose r larger than most of the noise. There is a preliminary conclusion given by Pincus (1991) that choices of r ranging from 0.1 to 0.2 SD of the u(i) data would produce reasonable statistical validity. In this research, r chooses 0.2 SD of the u(i) data, m chooses 2.

2.2 Volunteers

Studies were conducted on 4 healthy yellow males (Table 1). All volunteers were no smokers in good health, and none took any drugs during this period. They participated in regular physical training before the research, and were of average fitness. The volunteers refrained from heavy exercise and from consuming caffeinated or alcohol beverages for at lease 24 hours before the test. All subjects were sea-level residents, and none was acclimatized to above 3000m before the experiment.

Table 1. Main Biometrical Characteristics of the volunteers

N=4	Mean±SD
Age (year)	21±2
Height (cm)	172.5±5.6
Body mass (kg)	76.3±4.1
HR (N/min)	66±8

2.3 Study design

This study used an unblinded two-factor (test condition and group) experimental design. The test conditions were defined as different altitude, the groups were defined as rest and cycle training during IHE.

The training proceeded in a quiet, environmentally controlled laboratory at an ambient temperature of 19-21℃. By control the flowing ratio of nitrogen and air, hypoxia cabin was designed to simulate different altitude from 0-8000 meters. All the experiments lasted for 8 days, the simulated altitude was from 3000m, 3500m, 4000m to 4500m. 3000m and 3500m lasted 2 days, 4000m and 4500m lasted 3 days, as was shown in Figure. 1.

Each training lasted 130 minutes, it's divided into four periods: two rest periods of 30 minutes and 60 minutes, two exercise periods of 20 min, the rest and exercise periods were across, as was shown in Figure. 2. In hypoxia cabin, the volunteers completed rest measurement with sedentary position, and they performed exercise measurement by a power bicycle inside.

Measured R-R intervals were determined from the electrocardiogram, there's a HR data of one experiment in Fig. 3. HR data were sampled and stored for subsequent analysis. Arterial oxygen saturation SaO_2 was monitored by Radical-7, Masimo Company, USA, the SaO_2 probe was set on the right index finger.

2.4 Statistical analysis

To make sure the stability of signal, at rest HRV indices were calculated from the 5 min of the every resting sequence; at exercise, HRV indices were assessed from the second stationary 5 min of the 20-min period. To every chosen HRV data, the SampEn was calculated as introduced before.

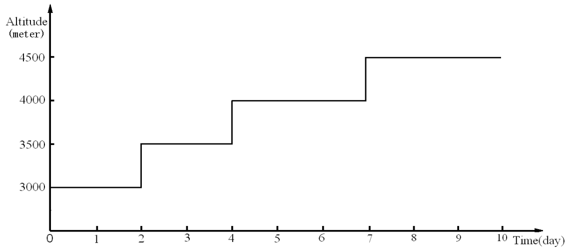

Figure 1. simulated altitude of every day

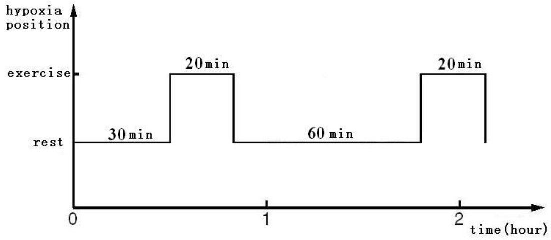

Figure 2. Schematic Diagram of Experiment Protocol

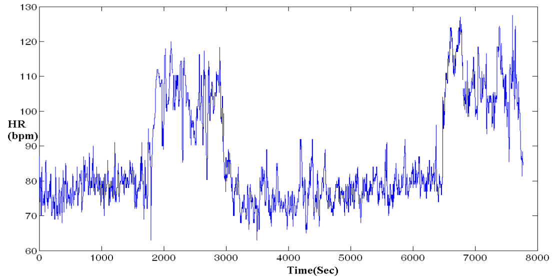

Figure 3. Heart Rate Data of one Experiment

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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 Contrast of different periods

The SampEn analysis of two different rest periods in one experiment showed there's no statistical difference between them. The same result was gotten between 2 different exercise periods either. At the same time, there was statistical difference between SampEn of the rest and exercise periods, as was shown in Table 2.

3.2 Contrast of different altitudes

The SampEn of different altitude was shown in Fig.5. To the rest periods, it decreased from 3000m to the second day of 4000m, then it increased from the third day of 4000m to 4500m. At the first six days, sample entropies decreased, while from the seventh day, sample entropies increased suddenly, and they were higher than the first day. To the exercise periods, the SampEn decreased at 3000m, then it increased slowly from 3500m to 4500m.

Table 2 SampEn of different periods

Altitude	Rest1	Rest2	Exer1	Exer2
3000m	0.76	0.76	0.89	0.88
3000m	0.75	0.75	0.87	0.86
3500m	0.73	0.74	0.88	0.88
3500m	0.73	0.75	0.87	0.89
4000m	0.73	0.73	0.90	0.90
4000m	0.72	0.73	0.87	0.88
4000m	0.76	0.77	0.91	0.91
4500m	0.78	0.78	0.90	0.90
4500m	0.77	0.77	0.93	0.91
4500m	0.78	0.77	0.93	0.93

4. Discussions

Noninvasive and real-time evaluation parameter of the autonomic nervous system can be performed by studying heart rate variability. HRV is the beat to beat alteration of the R-R intervals in an electrocardiogram, it's the consequence of heart rate modulation by both branches of the autonomic nervous system, and it's the most commonly used monitoring of autonomic nervous activities. Previous observati _onns on HRV suggest increased sympathetic and decreased parasympathetic modulation in altitude (Roche, 2002). 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 is increased at the same time.

Most studies measured autonomic nervous activity by assessing HRV by time or frequency domain (Foster, 2009; Bernardi L, 2001). 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.

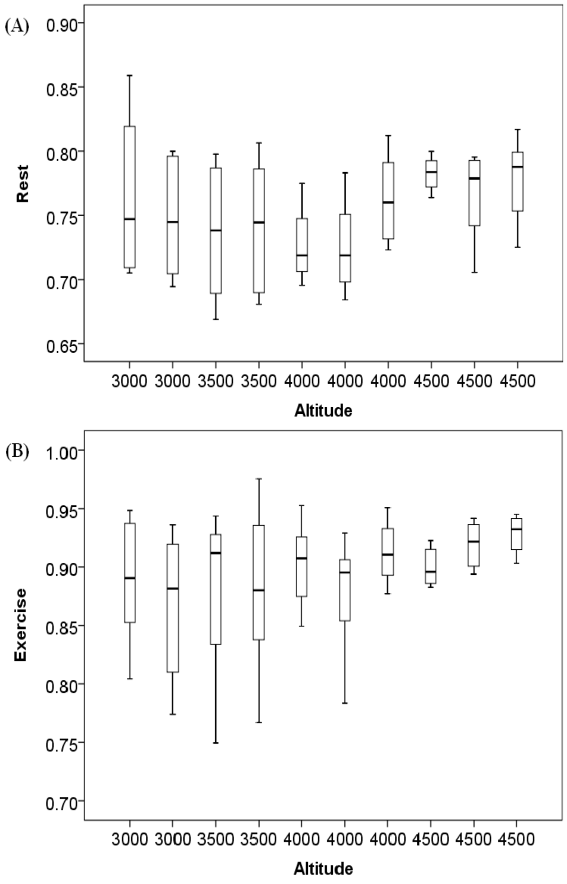

Figure 5. SampEn of different altitudes. (A). rest period, (B).exercise period

According to some researchers, the low responsiveness of the autonomic nervous system at high altitudes could mean an advantage in the protection of the organs against an excessive and uninterrupted sympathetic stimulation during a long stay at high altitudes. While others thought the reduction in the responsiveness of the autonomic nervous system could indicate an inability of the body to adapt to challenging conditions, such as exposure to hypobaric hypoxia.

Jason investigated the intermittent hypoxia and respiratory plasticity in humans and other animals, to make sure if exposure to intermittent hypoxia promote or mitigate sleep apnoea (Jason, 2009). Camilo Povea observed the changes in heart rate variability induced by an intermittent exposure to hypoxia in 20 national elite athletes, evaluated the difference between two groups: LLTL(live low, train low) and LHTL(live high, train low). They found exposure to acute hypoxia during exercise resulted in a significant decrease in spectral components of HRV in comparison with exercise in normoxia. Acclimatization modified the correlation between the ventilatory response to hypoxia at rest and the difference in total power between normoxia and hypoxia. The increase in total power, LF component, and LF/HF ratio suggests that intermittent hypoxic training increased the response of the autonomic nervous system mainly through increased sympathetic activity (Camilo, 2005). The purpose of Buchheit's study was to investigate sympathovagal balance as inferred from HRV responses to acute hypoxia at rest and during exercise. HRV was evaluated in subjects during a standardized hypoxic tolerance test, the exercise was moderate exercise. All absolute HRV indexes were strongly reduced during exercise with no further changes under additional stimulus of hypoxia. The result of his research indicate a vagal control withdrawal under hypoxia at rest, during exercise at 50% VO_2max, HRV indexes cannot adequately represent cardiac autonomic adaptation to acute hypoxia, or possibly to other additional stimuli, due to the dominate effect of exercise and the eventual influence of confounding factors (Buchheit, 2004). His research used the hypoxia veil, the result maybe had some difference with hypoxia chamber.

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 here. The main achievement of sample entropy is the simplicity of computation, and the showing of dynamical system components.

Acute exposure to normobaric hypoxia changes cardiovascular autonomic nerve modulation and balance. In this exam, these modulations were shown through the change of SampEn.

SampEn analysis of HRV is not sensitive to missing points, loss of data points is irrelevant to the calculation. They found SampEn little affected by loss of more than one-third of the data, the practical limit that everyone might encounter. It is surprising, since loss of small amounts of data significantly impaired the detection of regularity in truly deterministic data. The finding is consistent with other results presented here that SampEn of HR records reports on spikes as well as regularity. Frequency domain analysis of HRV dissects sympathetic and parasympathetic activity (Buchheit, 2004; Lake, 2002), but is very sensitive to missing data points(Berntson, 1998; Schechtman, 1988).

5. Conclusion

In this study, changes of HRV induced by stepwise exposure to hypoxia from 3000m to 4500m during rest and exercise were evaluate in healthy yellow males. We used SampEn to analysis HRV, the results of this study indicated that hypoxia per se affects the functioning of the autonomic nervous system under the simulated hypoxia conditions. SampEn and other nonlinear methods are useful tools to detect hypoxia acclimation. Further studies are needed to conform our results, especially to more subjects.

Acknowledgements:

This work is supported by 973 National Foundation of China (No. 2012CB518200).

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References

1. Hackett PH, Roach RC, High-altitude illness, New England Journal of Medicine, 2001, 345(2):107–113 .
2. World Health Organization. International travel and health, Geneva, Switzerland: WHO. 2005.
3. Iwasaki K., Aoki Ken, Saitoh Takashi, O. Akira, S. Shigeki. Cardiovascular Regulation Response to Hypoxia During Stepwise Decreases from 21% to 15% Inhaled Oxygen. Aviation, Space, and Environmental Medicine. 2006,77(10): 1015-1019.
4. Barron HV, Viskin S. Autonomic arkers and prediction of cardiac death after myocardial infarction. Lancet. 1998, 351:461-472.
5. Douglas E.L., Joshua S.R., M.Pamela G., J. Randall M. Sample entropy analysis of neonatal heart rate variability. American Journal of Physiology Regulatory, Integrative and Compar _ative Physiology. 2002, 283: R789–R797
6. M. Buchheit, R. Richard, S. Doutreleau. Effect of acute hypoxia on heart rate variability at rest and during exercise. International Journal of Sports Medicine. 2004, 25:264-269.
7. Saito S., K. Tanobe. Relationship between arterial oxygen saturation and heart rate variability at high attitudes. American Journal of Emergency Medicine, 2005, 23(1): 8-12.
8. Joshua S. R., J. Randall M. Physiological time-series analysis using approximate entropy and sample entropy. American Journal Physiology Heart Circular Physiology. 2000, 278: 2039-2049.
9. Pincus SM. Approximate entropy as a measure of system complexity. Proceedings of the National Academy of Sciences. 1991, 88: 2297-2301.
10. Roche F., Reynaud C., Garet M., Pichot V., Costes F., Barthélémy J.C. Cardiac baroreflex control in humans during and immediately after brief exposure to simulated high altitude Clinical Physiology Function Imaging. 2002, 22: 301–306.
11. Camilo Povea, L. Schmitt, Julien Brugniaux. Effects of Intermittent Hypoxia on Heart Rate Variability during Rest and Exercise. High Altitude Medicine& Biology. 2005, 6(3): 215-225.
12. Foster GE, McKenzie DC, Milsom WK, Sheel AW. Effects of two protocols of intermittent hypoxia on human ventilatory, cardiovascular and cerebral responses to hypoxia. Journal of Physiology. 2009,567(2):. 689–699
13. Bernardi L, Passino C, Serebrovskaya Z, Serebrovskaya T, Appenzeller O. Respiratory and cardiovascular adaptations to progressive hypoxia; effect of interval hypoxic training. European Heart Journal. 2001, 22(10): 879-886.
14. Jason H. Mateika, Gunjan Narwani, Interm-ittent hypoxia and respiratory plasticity in humans and other animals: does exposure to intermittent hypoxia promote or mitigate sleep apnoea? Experimental Physiology. 2009, 94(3): 279-296.
15. D.E. Lake, J.S. Richman, M.P. Griffin. Sample entropy analysis of neonatal heart rate variability. American Journal of Physiology Regulatory, Integrative and Comparative Physiology. 2002,283: R789–R797.
16. Berntson G.G. and Stowell J.R. ECG artifacts and heart period variability: don't miss a beat. Psychophysiology. 1998, 35: 127–132.
17. Schechtman VL, Kluge KA, and Harper RM. Time domain system for assessing variations in heart rate. Medical Biological Engineering Computing. 1988, 26: 367–373.

8/7/2013