Journal of Clinical & Experimental Cardiology

Wang et al., J Clin Exp Cardiolog 2015, 6:1
DOI: 10.4172/2155-9880.1000357

Research Article Open Access

Low-altitude Mountain Tourism Increases Overall Heart Rate Variability and Decreases Heart Rate and Blood Pressures in Healthy Adults

Chen-Hsu Wang[1-3], **Audrey Ming-Li Fan**[1], **Chen Lin**[4,5] and **Cheng-Deng Kuo**[1*]

[1]*Laboratory of Biophysics, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan*

[2]*Graduate Institute of Translational and Interdisciplinary Medicine, National Central University, Taoyuan, Taiwan*

[3]*Medical Intensive Care Unit, Division of Cardiology, Department of Internal Medicine, Cathay General Hospital, Taipei, Taiwan*

[4]*Research Center for Adaptive Data Analysis, National Central University, Taoyuan, Taiwan*

[5]*Center for Dynamical Biomarkers and Translational Medicine, National Central University, Taoyuan, Taiwan*

[*]**Corresponding author**: Cheng-Deng Kuo, Laboratory of Biophysics, Department of Medical Research, Taipei Veterans General Hospital, Taipei 112, Taiwan; Tel-886228757745; E-mail: cdkuo23@gmail.com

Received date: December 22, 2014; **Accepted date:** January 28, 2015; **Published date:** January 31, 2015

Abstract

Background: People often feel comfort and relaxation during low-altitude mountain tourism below 1500 meters above sea level (MASL). But the real effects of low-altitude mountain tourism on humans are not well understood.

Methods: Three different low-altitude locations (30, 520 and 1080 MASL) were chosen for Heart Rate Variability (HRV) and hemodynamic analyses in 49 healthy adults.

Results: The Heart Rate (HR) and Blood Pressures (BP) were decreased, whereas the Standard Deviation (SD_{RR}) and Coefficient of Variation (CV_{RR}) of RR intervals, Total Power (TP), Low-Frequency Power (LFP) and High-Frequency Power (HFP) of HRV were increased at 520 and 1080 MASL, as compared with those at 30 MASL. The age of subjects correlated negatively with SD_{RR}, CV_{RR}, TP and HFP, and correlated positively with normalized very-low-frequency power as altitude increased. Male subjects had a higher SD_{RR}, CV_{RR}, TP and LFP at 520 MASL, and a lower Systolic Blood Pressure (SBP) at 1080 MASL. The SBP, mean arterial blood pressure and pulse pressure were significantly decreased when the old subjects ascended from 30 MASL to a higher altitude. This phenomenon was not found in the young subjects. The BP of the old subjects can be decreased to more extent than the young subjects by traveling in the low-altitude mountain area.

Conclusion: Low-altitude wilderness tourism within 1080 MASL can lead to a decrease in HR and BP, and an increase in overall HRV. The greatest decrease in HR and BP and the greatest increase in overall HRV occur at around 520 MASL. Male subjects have higher overall HRV and low-frequency components than females at 520 MASL. Travel in low-altitude mountain area may be good to physiological fitness for healthy adults in terms of automatic nervous modulation and blood pressure regulation, especially in the older people.

Keywords: Altitude; Heart rate variability; Heart rate; Blood pressures; Autonomic nervous system

Introduction

Wilderness tourism is popular all over the world. But travellers exposed to high-altitudes could result in severe illness [1]. Previous studies indicated that acute mountain sickness (AMS) can occur to trekkers during rapid ascent when they were exposed to low partial pressure oxygen at altitudes higher than 1500 meters above sea level (MASL) [2]. Even with only trivial to mild non-specific symptoms, most AMS victims have autonomic nervous modulation dysfunction [3].

Different with high-attitude trekkers, most sea-level residents seldom travel to the altitudes higher than 1500 MASL. That is, most people living in the "near sea-level area" (between 0 and 500 MASL) often enjoy their weekend vacations in the "low-altitude area" (between 500 and 1500 MASL) [4]. Contrary to the possible illness at higher altitudes, most sea-level residents seem to experience more relaxation and comfort in their "low-altitude" mountain tourism [5]. The feeling of comfort and relaxation usually result from parasympathetic enhancement which is often associated with better physiological fitness [6] and better prognosis in disease [7].

Heart Rate Variability (HRV) analysis is a non-invasive and quantitative method that can be used to assess the autonomic nervous control of the heart rate [8-10]. Current evidence has found that travellers at altitudes higher than 1500 MASL have profound changes in HRV, such as dominant low-frequency power, increased low-/high-frequency power ratio, and decreased autonomic nervous modulation [11]. However, few studies have focused on the effect of low-altitude exposure on human autonomic nervous regulation in mountain tourism [12,13].

Since many travellers in low-altitude area experience feelings opposite to those AMS victims at higher altitudes, the aim of this study was to observe the acute effects of altitude ascent on the blood pressures and autonomic nervous modulation in health subjects in the low-altitude area (below 1500 MASL) during mountain tourism.

Methods

Study subjects and sampling altitudes

This study was conducted in the Yang-Ming-Shan National Park (YMSNP) located at northern Taiwan and near Taipei. The YMSNP summit is the highest peak in Taipei with a height of 1120 MASL. Three different altitudes in wilderness were chosen from Google Map for study. The first location categorized as "near sea-level" [4] was 30 MASL (location A). The 2nd and 3rd locations categorized as "low-altitude" [4] had altitudes 520 MASL (location B) and 1080 MASL (location C), respectively. The location A and location C were chosen because they are the lowest and the highest altitudes within YMSNP which are suitable for study, respectively. The intermediate altitude at location B was chosen because it is located midway between locations A and C, and is close to the "low-altitude" (500 MASL) defined by Bartsch and Saltin [4]. These 3 locations were all quiet wilderness places with comfortable mountain breeze that can easily be reached by general public traffic.

Healthy adult sea-level residents were recruited from the community. Those subjects who had the following factors were excluded: (1) surgical operation within one year; (2) history of diabetes, hypertension, asthma, arrhythmia or autonomic neuropathy; (3) history of AMS; (4) recent mountain tourism above 1500 MASL for longer than one week and (5) active menstruation period in female.

The Institutional Review Board of the Hospital has approved this study, and a written informed consent was obtained from each subject before enrolment.

Study protocol

Every subject was introduced to the study protocol before the study and was requested to refrain from alcohol, caffeine intake within 24 hours prior to altitude exposure. Basic characteristics, including body weight, body height and body mass index, were collected before the study. Then each subject was transported to locations A, B and C by same car for the collection of necessary physiological signals at 3 different altitudes in good climate. The time needed for transportation from location A to location B, and from location B to location C, was about 30 minutes by car in the morning, respectively. Every subject was requested to void before study and not to take food or water during the study period in the YMSNP.

At each location, the car was parked at the same position without direct sunshine and wind blowing. Each subject was requested to take a 5-minute slow walk around to relieve the sedentary tension during traffic, and then sit comfortably in the back seat of the car with all doors and windows suitably opened. After 10-minute eyes-closed rest in sitting position, preliminary physical check-up and physiological signal was collected on each subject. The body temperature of the subject was recorded by a non-contact infrared forehead thermometer (HM-8877, Hers Medical Co., Ltd. Taiwan). The Heart Rate (HR), Systolic (SBP) and Diastolic (DBP) Blood Pressures of the subject were measured at the right arm by using a validated automatic sphygmomanometer (HEM-770A, Omron Inc., Japan) [14] for 3 times with a 30-second interim period. The Mean Arterial Blood Pressure (MABP) and Pulse Pressure (PP) were calculated from the SBP and DBP by using standard formulae. The data of these 3 measurements were averaged for later analysis [15]. Environmental factors were measured by a portable temperature and humidity instrument (HygroPalm 0, Rotronic AG, Switzerland) at the same time.

HRV analysis

Then all subjects were requested to keep rest with their eyes closed. A trend of Electrocardiographic (ECG) signals was retrieved by a physiological signals acquisition apparatus (Biopac MP35, Biopac Systems, Inc., USA) with 500 Hz sampling frequency, and transmitted to a laptop computer for recording for 12 minutes. The analog ECG signals were digitalized by data acquisition converter (AcqKnowledge 3.9; Biopac Systems, Inc., USA). The peaks of the R wave were identified by an algorithm of parabolic interpolation and a derivative plus threshold algorithm (Matlab 6.5; MathWorks Inc., Natick, MA, USA) after the cardiologist had reviewed the recorded ECG. The cardiologist identified the ectopic beats, arrhythmic events, missing data, and noise to delete the possible error in R wave identification. The last 512 stationary RR intervals (RRI) were used for HRV analysis. If the percentage of deletion was >5%, then the subject were excluded from the study.

The time domain HRV measures included mean RRI (mRRI), Standard Deviation of RRI (SD_{RR}) and Coefficient of Variation of RRI (CV_{RR}) [16]. The frequency domain HRV measures were obtained by transforming the 512 RRI into power spectrum using fast Fourier transformation (Mathcad, Mathsoft Inc., Cambridge, MA, USA). The area under the spectral peaks in the RRI spectrum within the range of 0.01-0.04, 0.04-0.15, 0.15-0.4, and 0.01-0.4 Hz were defined as Very-Low-Frequency Power (VLFP), Low-Frequency Power (LFP), High-Frequency Power (HFP), and Total Power (TP), respectively [17]. The normalized HFP (nHFP=HFP/TP) was used as the index of vagal modulation, the normalized LFP (nLFP=LFP/TP) as the index of combined vagal and sympathetic modulations, the low-/high-frequency power ratio (LHR=LFP/HFP) as the index of sympathovagal balance [16,18], and the normalized VLFP (nVLFP=VLFP/TP) as the index of renin-angiotensin-aldosterone modulation and vagal withdrawal of the subject [19,20], or the index of thermoregulation [21].

Data analysis

Data are presented as median and interquartile range (IQR, 25th to 75th percentiles) owing to the fact that nearly all HRV measures are not normally distributed, as verified by using Shapiro-Wilk test or Kolmogorov-Smirnov test. Friedman repeated-measures analysis of variance on ranks with Student-Newman-Keuls test for post hoc comparisons was employed to compare the clinical data, the HRV measures among 3 different altitudes, and the percentage changes in HRV measures between different altitudes. The Mann-Whitney rank sum test was used to compare the general characteristics of the subjects and HRV measures between groups.

The percentage changes in blood pressures and HRV measures between different altitudes were calculated by using the following formulae, where "X" stands for the blood pressures and HRV measure to be analysed:

Ascent from 30 to 520 MASL = $\%X_{30\text{-}520} = 100\% \cdot (X_{520}\text{-}X_{30})/X_{30}$

Ascent from 520 to 1080 MASL = $\%X_{520\text{-}1080} = 100\% \cdot (X_{1080}\text{-}X_{520})/X_{520}$

Ascent from 30 to 1080 MASL = $\%X_{30\text{-}1080} = 100\% \cdot (X_{1080}\text{-}X_{30})/X_{30}$

Spearman rank order correlation was used to evaluate the relationship between general characteristics of subjects and environmental factors. All statistical analyses were performed using

SigmaPlot 12.5 (SPSS Inc., Chicago, IL, USA). A $p<0.05$ was considered statistically significant.

Results

General characteristics of participants

Forty-nine healthy subjects (M/F=21/28, aged 20-60 years) were included in this study. All subjects felt relaxed during the low-altitude tourism without any discomfort.

Blood pressures, HRV measures and environmental factors at 3 altitudes

The SBP, MABP, PP, and HR of the subjects at altitudes 520 and 1080 MASL were significantly decreased, while the mRRI, SD_{RR}, CV_{RR}, TP, VLFP, LFP and HFP of the subjects at altitudes 520 and 1080 MASL were significantly increased, as compared with their counterparts at altitude 30 MASL (Table 1).

	30 MASL	520 MASL	1080 MASL	p
Gender (M/F)	21/28	-	-	-
Age (year)	31 (26-51)	-	-	-
Height (cm)	163 (158-170)	-	-	-
Weight (kg)	62 (50-70)	-	-	-
BMI (kg/m^2)	23.0 (20.5-24.8)	-	-	-
BT (°C)	36.5 (36.0-36.9)	36.5 (36.3-36.7)	36.4 (35.9-36.8)	0.87
SBP (mmHg)	113 (107-125)	111 (103-120)*	108 (100-116)*†	0.002
DBP (mmHg)	73 (68-79)	71 (68-77)	70 (66-75)	0.153
MABP (mmHg)	87 (82-92)	84 (81-90)*	83 (77-88)*	0.022
PP (mmHg)	42 (36-50)	39 (33-47)*	36 (33-42)*	0.014
HR (bpm)	74 (68-80)	69 (64-78)*	70 (64-77)*	<0.001
mRRI (ms)	812 (747-885)	869 (768-937)*	863 (784-937)*	<0.001
SD_{RR} (ms)	33 (26-43)	39 (32-52)*	42 (32-58)*	<0.001
CV_{RR} (%)	4.2 (3.3-5.3)	4.9 (4.0-5.8)*	4.7 (3.9-6.2)*†	0.002
TP (ms^2)	449 (247-761)	624 (367-1088)*	578 (409-1199)*	<0.001
VLFP (ms^2)	158 (70-260)	189 (126-316)*	174 (134-357)*	0.002
LFP (ms^2)	110 (53-275)	189 (93-377)*	200 (92-318)*	0.018
HFP (ms^2)	166 (68-300)	214 (101-389)*	196 (99-370)*	0.012
nVLFP (nu)	32.7 (23.8-46.4)	34.0 (21.8-43.8)	33.2 (24.2-48.2)	0.352
nLFP (nu)	30.2 (20.6-39.2)	31.0 (24.6-39.5)	28.0 (22.6-37.6)	0.6
nHFP (nu)	29.2 (22.2-47.0)	32.6 (21.4-43.4)	30.8 (21.4-45.2)	0.416
LHR	1.0 (0.5-1.5)	0.9 (0.6-1.6)	1.1 (0.5-1.8)	0.312
AT (°C)	31 (28-33)	30 (28-31)	30 (28-33)	0.205
RH (%)	58 (51-67)	62 (54-66)	55 (49-64)*†	<0.001

Table 1: General characteristics of the study subjects, blood pressures, HRV measures and environmental conditions at 3 different altitudes (n=49). Values are median and interquartile range (25th to 75th percentile). *p<0.05 vs. 30 MASL; †p<0.05 vs. 520 MASL (Friedman repeated-measures analysis of variance on ranks with Student-Newman-Keuls test for post hoc pairwise comparisons). BMI: Body mass index; HR: Heart rate; RRI: RR intervals; mRRI: Mean RRI; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MABP: Mean arterial pressure; BT: Body temperature; bpm: Beats per minute; SD_{RR}: Standard deviation of RRI; CV_{RR}: Coefficient of variation of RRI; TP: Total power; VLFP: Very-low-frequency power; LFP: Low-frequency power; HFP: High-frequency power; nVLFP: Normalized VLFP; nLFP: Normalized LFP; nHFP: Normalized HFP; LHR: Low-/high-frequency power ratio; ms: Millisecond; nu: Normalized unit; AT: Ambient temperature; RH: Relative humidity.

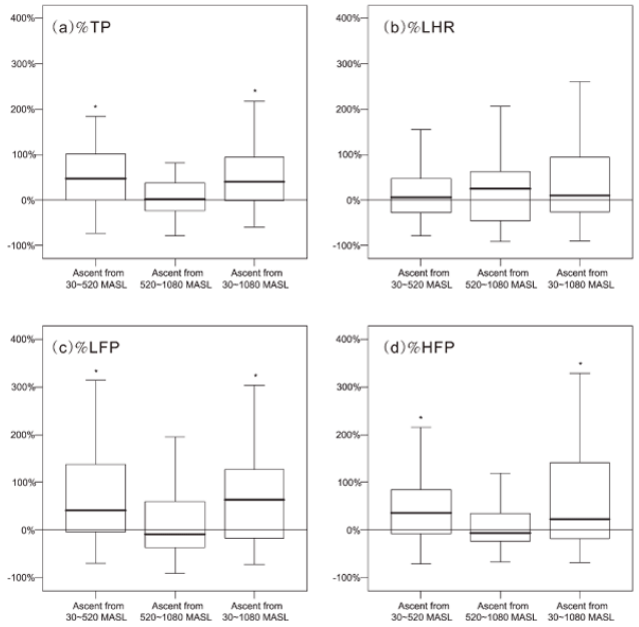

Figure 1: Percentage changes in HRV measures of total power (a, %TP); low-/high- frequency power ratio (b, %LHR); low frequency power (c, %LFP) and high frequency power (d, %HFP) among different altitude ascents, respectively. *p<0.05 vs. Ascent from 520 to 1080 MASL. Box represent median and IQR (interquartile range, 25th to 75th percentile), whiskers represent maximum 1.5 IQR values of upper and lower quartile.

Furthermore, the SBP of the subjects at altitude 1080 MASL was significantly lowered as compared with that at altitude 520 MASL, and the CV_{RR} at 1080 MASL was significantly lower than that at 520 MASL. The relative humidity at 1080 MASL was significantly lower than that at the other 2 altitudes. However, the body temperature, DBP, normalized HRV measures, LHR and ambient temperature were not significantly different among 3 altitudes.

The percentage increases in TP, LFP and HFP due to ascent from 30 MASL to 520 MASL and from 30 MASL to 1080 MASL were significantly larger than those due to ascent from 520 MASL to 1080 MASL (Figure 1). No significant difference among the percentage changes in LHR between 3 kinds of altitude change was found in this study.

Linear correlation analysis showed that when the subjects ascended from 30 MASL to 520 MASL, the percentage change in HR correlated significantly and negatively with the percentage changes in HFP and nHFP and correlated significantly and positively with the percentage changes in LHR (Table 2). When the subjects ascended from 30 MASL to 1080 MASL, the percentage change in HR correlated significantly and negatively with the percentage changes in SD_{RR}, CV_{RR}, TP, LFP, HFP and nHFP, and correlated significantly and positively with the percentage changes in LHR (Table 3).

There were no correlation between the percentage changes in SBP, DBP, MABP, PP, RH and the percentage changes in SD_{RR}, CV_{RR}, TP, VLFP, LFP, HFP, nVLFP, nLFP, nHFP, LHR (Tables 2 and 3).

This result suggested that the changes in HRV measures were not related directly to the changes in blood pressures of the subjects or the humidity of the environment, implying that the blood pressures of the subjects are controlled by multiple factors, not limited to autonomic nervous modulation.

These results suggested that a larger increase in vagal modulation and a larger decrease in sympathetic modulation caused by traveling to a higher altitude are associated with a smaller decrease in heart rate, and vice versa.

	%$SD_{RR\ 30\text{-}520}$	%$CV_{RR30\text{-}520}$	%$TP_{30\text{-}520}$	%$VLFP_{30\text{-}520}$	%$LFP_{30\text{-}520}$	%$HFP_{30\text{-}520}$	%$nVLFP_{30\text{-}520}$	%$nLFP_{30\text{-}520}$	%$nHFP_{30\text{-}520}$	%$LHR_{30\text{-}520}$
%$HR_{30\text{-}520}$	0.009 R= -0.367	0.241	0.071	0.82	0.323	<0.001 R= -0.636	0.258	0.313	0.004 R= -0.404	0.032 R=0.307
%$SBP_{30\text{-}520}$	0.326	0.293	0.362	0.8	0.217	0.901	0.737	0.25	0.18	0.149
%$DBP_{30\text{-}520}$	0.124	0.293	0.332	0.76	0.304	0.096	0.902	0.202	0.982	0.714
%$MABP_{30\text{-}520}$	0.12	0.21	0.266	0.73	0.185	0.231	0.84	0.132	0.503	0.624
%$PP_{30\text{-}520}$	0.9	0.831	0.827	0.99	0.734	0.432	0.637	0.796	0.405	0.272
%$RH_{30\text{-}520}$	0.525	0.383	0.294	0.34	0.559	0.561	0.915	0.979	0.484	0.737

Table 2: The p values and Pearson correlation coefficients of linear regression between the percentage changes in heart rate, blood pressures and relative humidity of the environment and the percentage changes in HRV measures when the subjects ascended from 30 MASL to 520 MASL (n=49). HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MABP: Mean arterial blood pressure; PP: Pulse pressure; RH: Relative humidity; SD_{RR}: Standard deviation of RRI; CV_{RR}: Coefficient of variation of RRI; TP: Total power; VLFP: Very-low-frequency power; LFP: Low-frequency power; HFP: High-frequency power; nVLFP: Normalized VLFP; nLFP: Normalized LFP; nHFP: Normalized HFP; LHR: Low-/high-frequency power ratio.

	%$SD_{RR30\text{-}1080}$	%$CV_{RR30\text{-}1080}$	%$TP_{RR30\text{-}1080}$	%$VLFP_{RR30\text{-}1080}$	%$LFP_{RR30\text{-}1080}$	%$HFP_{RR30\text{-}1080}$	%$nVLFP_{30\text{-}1080}$	%$nLFP_{30\text{-}1080}$	%$nHFP_{30\text{-}1080}$	%$LHR_{30\text{-}1080}$
%$HR_{30\text{-}1080}$	<0.001 R= -0.628	0.003 R= -0.411	<0.001 R= -0.465	0.054	0.033 R= -0.305	<0.001 R= -0.687	0.501	0.139	0.001 R= -0.451	0.047 R= 0.286
%$SBP_{30\text{-}1080}$	0.974	0.948	0.67	0.946	0.73	0.555	0.946	0.73	0.555	0.448
%$DBP_{30\text{-}1080}$	0.734	0.922	0.961	0.174	0.277	0.217	0.174	0.277	0.217	0.605
%$MABP_{30\text{-}1080}$	0.766	0.895	0.899	0.346	0.539	0.234	0.346	0.539	0.234	0.989
%$PP_{30\text{-}1080}$	0.709	0.885	0.524	0.336	0.345	0.689	0.336	0.345	0.689	0.3
%$RH_{30\text{-}1080}$	0.761	0.734	0.766	0.204	0.94	0.158	0.061	0.937	0.157	0.659

Table 3: The p values and Pearson correlation coefficients of linear regression between the percentage changes in heart rate, blood pressures and relative humidity of the environment and the percentage changes in HRV measures when the subjects ascended from 30 MASL to 1080 MASL (n=49). HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MABP: Mean arterial blood pressure; PP: Pulse pressure; RH: Relative humidity; SD_{RR}: Standard deviation of RRI; CV_{RR}: Coefficient of variation of RRI; TP: Total power; VLFP: Very-low-frequency power; LFP: Low-frequency power; HFP: High-frequency power; nVLFP: Normalized VLFP; nLFP: Normalized LFP; nHFP: Normalized HFP; LHR: Low-/high-frequency power ratio.

Age difference in blood pressures and HRV measures at 3 altitudes

The age of the subjects correlated significantly and negatively with SD_{RR}, CV_{RR}, TP, and HFP at 30, 520 and 1080 MASL. In contrast, the age correlated significantly and positively with the nVLFP at 3 altitudes (Table 4). These results indicated that older subjects had smaller SD_{RR}, CV_{RR}, TP, and HFP, but a larger nVLFP, no matter what altitude they were located at.

	SD_{RR}	CV_{RR}	TP	VLFP	LFP	HFP	nVLFP	nLFP	nHFP	LHR
30 MASL	0.005 R= -0.394	0.003 -0.42	0.017 -0.34	0.191	0.0634	0.0149 R= -0.346	0.003 R= 0.410	0.421	0.0537	0.361
520 MASL	0.006 R= -0.383	<0.001 R= -0.467	0.023 R= -0.323	0.242	0.019 R= -0.334	0.0496 R= -0.282	<0.001 R= 0.541	0.0536	0.0722	0.903
1080 MASL	0.0121 R= -0.356	0.002 R= -0.430	0.0141 R= -0.349	0.626	0.0477 R= -0.284	0.008 R= -0.375	<0.001 R= 0.587	0.351	0.002 R= -0.424	0.082

Table 4: The p values and Pearson correlation coefficients of linear correlation between the age and the HRV measures of the subjects at 3 altitudes (n=49) SD_{RR}: Standard deviation of RRI; CV_{RR}: Coefficient of variation of RRI; TP: Total power; VLFP: Very-low-frequency power; LFP: Low-frequency power; HFP: High-frequency power; nVLFP: Normalized VLFP; nLFP: Normalized LFP; nHFP: Normalized HFP; LHR: Low-/high-frequency power ratio.

The median age of the participants was 31 years old. Therefore, we stratified the subjects into two groups, the young and old groups, by using the median age as the dividing point. Subjects with age greater than 31 years were stratified as the old group, and subjects with age equal to and less than 31 years were stratified as the young group. The body height of the old group was smaller than that of the young group (Table 5). This is comprehensible because the young people were grown up in a better socio-economic environment than the old people.

The old people had smaller SD_{RR}, CV_{RR}, VLFP, LFP, and HFP nearly at all 3 locations in the mountain than those of the young group (Table 5). This was in accordance with the current understanding that ageing is associated with a reduced HRV at all frequencies. Though the nVLFP was not significantly different between the young and old groups at 30 MASL, it was significantly increased at 520 and 1080 MASL in the old group. Also, though the nHFP was not significantly different between the young and old groups at 30 MASL, it was significantly decreased at 520 MASL in the old group.

	30 MASL	520 MASL	1080 MASL	p
Young group (n=25)	-	-	-	-
Gender (M/F)	11/14	-	-	-
Age (yr)	26.0 (24.0-28.0)	-	-	-
Height (cm)	165 (160-174)	-	-	-
Weight (kg)	63 (54-72)	-	-	-
BMI (kg/m^2)	23.3(19.6-25.1)	-	-	-
SBP (mmHg)	115 (108-126)	113 (104-122)	110 (101-120)	0.165
DBP (mmHg)	73 (68-78)	71 (69-79)	70 (66-76)	0.756
MABP (mmHg)	88 (82-92)	85 (81-94)	83 (76-92)	0.326
PP (mmHg)	42 (35-51)	38 (33-50)	36 (32-48)	0.272
HR (bpm)	73 (67-80)	67 (63-78)*	71 (63-77)*	0.003
Mean RRI (ms)	827 (754-889)	896 (768-951)*	850 (778-948)*	0.003
SD_{RR} (ms)	40 (29-60)	48 (38-57)*	48 (39-64)*	0.021
CV_{RR} (%)	4.8 (3.9-6.9)	5.4 (4.8-6.4)	5.8 (4.5-7.1)	0.08
TP (ms^2)	698 (351-1201)	778 (567-1349)*	899 (528-1612)*	0.013
VLFP (ms^2)	196 (113-297)	237 (139-334)	217 (143-383)	0.21
LFP (ms^2)	145 (94-369)	227 (147-581)*	242 (131-524)*	0.024
HFP (ms^2)	240 (112-443)	323 (187-588)	308 (166-530)	0.228
nVLFP (nu)	31.3 (20.1-39.6)	26.0 (20.3-36.6)	27.8 (22.9-35.3)	0.887
nLFP (nu)	31.0 (20.4-38.5)	33.4 (24.5-43.4)	32.8 (22.3-43.6)	0.289
nHFP (nu)	42.1 (23.6-52.5)	38.3 (29.4-47.5)	33.9 (27.3-53.6)	0.756
LHR	0.77 (0.43-1.46)	0.81 (0.54-1.47)	0.93 (0.39-1.44)	0.326
Old group (n=24)	-	-	-	-
Gender (M/F)	10/14	-	-	-
Age (yr)	51.5 (36.8-54.8)§	-	-	-
Height (cm)	161 (156-168)§	-	-	-
Weight (kg)	61 (50-65)	-	-	-
BMI (kg/m^2)	22.5 (20.6-24.6)	-	-	-
SBP (mmHg)	113 (107-123)	110 (101-117)	106 (100-114)*†	0.003
DBP (mmHg)	73 (68-79)	71 (66-75)	71 (65-74)	0.115
MABP (mmHg)	86 (80-95)	84 (80-87)*	83 (77-87)*	0.05
PP (mmHg)	40 (35-46)	39 (32-45)	37 (33-42)*	0.036
HR (bpm)	75 (68-81)	70 (65-78)*	69 (64-76)*	<0.001

Mean RRI (ms)	796 (744-883)	858 (765-924)*	873 (793-941)*	<0.001
SD_{RR} (ms)	31 (21-39)§	36 (29-44)*§	34 (30-46)*§	0.008
CV_{RR} (%)	3.7 (2.6-4.7)§	4.1 (3.4-5.1)*§	4.0 (3.5-5.2)*§	0.009
TP (ms^2)	272 (154-555)§	491 (308-685)*§	488 (252-687)*§	0.011
VLFP (ms^2)	87 (50-200)§	166 (112-304)*	163 (122-330)*	0.002
LFP (ms^2)	89 (34-152)§	118 (73-250)§	137 (64-212)§	0.453
HFP (ms^2)	79 (36-178)§	136 (50-223)*§	114 (44-211)§	0.034
nVLFP (nu)	32.9 (27.6-52.3)	40.8 (32.3-52.1)§	47.5 (30.1-52.6)§	0.223
nLFP (nu)	29.5 (21.0-40.7)	27.9 (21.2-37.2)	27.5 (23.9-37.2)	0.959
nHFP (nu)	27.8 (21.6-37.6)	30.7 (17.4-35.3)§	22.3 (15.0-39.4)	0.079
LHR	1.12 (0.68-1.65)	0.96 (0.70-1.88)	1.25 (0.62-2.65)	0.275

Table 5: General characteristics, blood pressures, and HRV measures of young and old subjects at 3 altitudes. Values are median and interquartile range (25^{th} to 75^{th} percentile). *p<0.05 vs. 30 MASL; †p<0.05 vs. 520 MASL (Friedman repeated-measures analysis of variance on ranks with Student-Newman-Keuls test for post hoc pairwise comparisons). §p<0.05 vs. young group (Mann-Whitney rank sum test). BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MABP: Mean arterial blood pressure; PP: Pulse pressure; HR: Heart rate; RRI: RR intervals; mRRI: mean RRI; SDRR: Standard deviation of RRI; CVRR: Coefficient of variation of RRI; TP: Total power; VLFP: Very-low-frequency power; LFP: Low-frequency power; HFP: High-frequency power; nVLFP: Normalized VLFP; nLFP: Normalized LFP; nHFP: Normalized HFP; LHR: Low-/high-frequency power ratio; ms: Millisecond; nu: Normalized unit.

When the subjects ascended from 30 to 520 and 1080 MASL, the HR was significantly reduced, while the mRRI, SD_{RR}, TP and HFP were significantly increased in both young and old groups. In the old group only, the SBP was significantly decreased when the subjects ascended to from 30 to 1080 MASL, and from 520 to 1080 MASL. In addition, the MABP was significantly decreased when the subjects ascended from 30 to 520 and 1080 MASL, and the PP was significantly decreased when the subjects ascended from 30 to 1080 MASL in the old group.

Gender difference in blood pressures and HRV measures at 3 altitudes

The median and IQR (25^{th} to 75^{th} percentile) of age in males and females were 31 (26 to 54) and 33 (26 to 50), respectively (Table 6). No age difference was found between genders. The female subjects had a smaller body height and a smaller BMI than the male subjects, as expected. The SBP, DBP, MABP, and PP of the female subjects were nearly all significantly smaller than those of the male subjects at 3 altitudes, except the DBP at 30 MASL. Though not significantly different from those of the male subjects, the SD_{RR}, CV_{RR}, TP and LFP of the female subjects were all significantly smaller than those of male subjects at 520 MASL. There were no significant differences in all HRV measures between genders at 30 and 1080 MASL.

Male (n=21)	**30 MASL**	**520 MASL**	**1080 MASL**	**p**
Age (year)	31 (26-54)	-	-	-
Height (cm)	171 (168-177)	-	-	-
Weight (kg)	72 (63-79)	-	-	-
BMI (kg/m^2)	24.1 (23.0-25.9)	-	-	-
SBP (mmHg)	124 (115-132)	118 (112-129)	115 (109-127)*†	0.025
DBP (mmHg)	75 (70-81)	72 (70-82)	74 (71-79)	0.918
MABP (mmHg)	90 (86-98)	89 (84-95)	87 (84-96)	0.244
PP (mmHg)	50 (42-54)	44 (38-50)	40 (34-50)	0.046
HR (bpm)	71 (69-76)	67 (61-77)*	66 (63-75)*	0.006
mRRI (ms)	848 (789-874)	899 (782-989)*	908 (798-947)*	0.006
SD_{RR} (ms)	41 (25-60)	47 (39-57)*	43 (37-59)*	0.028
CV_{RR} (%)	4.8 (3.1-7.0)	5.2 (4.7-6.1)	5.0 (4.0-6.2)	0.084
TP (ms^2)	714 (228-1049)	737 (537-1322)*	680 (527-1280)*	0.018
VLFP (ms^2)	196 (84-328)	244 (158-355)	262 (151-424)	0.156
LFP (ms^2)	123 (53-419)	354 (122-538)	222 (141-459)	0.229
HFP (ms^2)	208 (48-413)	222 (120-480)	219 (130-497)	0.156
nVLFP (nu)	33.1 (24.4-40.9)	34.0 (21.2-42.0)	31.7 (25.5-44.4)	0.538

nLFP (nu)	31.0 (20.6-39.6)	33.4 (26.2-44.8)	30.1 (25.4-40.7)	0.717
nHFP (nu)	27.5 (22.1-47.2)	30.2 (13.9-43.6)	28.9 (20.9-45.5)	0.867
LHR (%)	1.3 (0.6-1.8)	1.1 (0.7-3.2)	1.2 (0.5-1.9)	0.405
Female (n=28)				
Age (year)	33 (26-50)	-	-	-
Height (cm)	158 (154-162)§	-	-	-
Weight (kg)	52 (49-59)§	-	-	-
BMI (kg/m^2)	21.1 (19.5-23.3)§	-	-	-
SBP (mmHg)	110 (103-113)§	104 (100-113)§	102 (100-108)§	0.057
DBP (mmHg)	72 (67-77)	70 (66-73)§	68 (64-72)§	0.07
MABP (mmHg)	83 (79-90)§	82 (79-85)§	79 (76-84)§	0.087
PP (mmHg)	37 (33-42)§	35 (30-41)§	35 (30-41)§	0.062
HR (bpm)	76 (67-83)	70 (65-78)*	72 (65-77)*	<0.001
mRRI (ms)	793 (720-891)	858 (768-923)*	836 (782-927)*	<0.001
SD_{RR} (ms)	32 (26-38)	38 (29-47)*§	38 (31-53)*	0.004
CV_{RR} (%)	4.1 (3.5-4.8)	4.3 (3.6-5.2)§	4.5 (3.8-6.1)*	0.019
TP (ms^2)	379 (260-553)	569 (322-784)*§	525 (354-955)*	0.004
VLFP (ms^2)	131 (63-201)	159 (114-261)*	157 (123-302)*	0.01
LFP (ms^2)	109 (60-159)	138 (85-232)§	150 (89-281)	0.069
HFP (ms^2)	91 (77-229)	201 (101-314)	191 (79-309)	0.074
nVLFP (nu)	31.0 (21.0-51.5)	33.8 (24.5-44.1)	34.2 (24.1-49.7)	0.629
nLFP (nu)	26.9 (20.8-38.2)	27.5 (22.0-36.7)	26.7 (21.3-36.5)	0.779
nHFP (nu)	30.0 (23.1-47.1)	33.7 (29.1-43.7)	31.0 (21.6-46.2)	0.368
LHR (%)	0.9 (0.5-1.4)	0.8 (0.6-1.2)	1.1 (0.5-1.4)	0.507

Table 6: General characteristics, blood pressures and HRV measures of male and female subject at 3 altitudes. Values are median and interquartile range (25th to 75th percentile). *p<0.05 vs. 30 MASL; †p<0.05 vs. 520 MASL (Friedman repeated-measures analysis of variance on ranks with Student-Newman-Keuls test for post hoc pairwise comparisons). §p<0.05 vs. male subjects (Mann-Whitney rank sum test). BMI: Body mass index; HR: Heart rate; RRI: RR intervals; mRRI: Mean RRI; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MABP: Mean arterial pressure; BT: Body temperature; bpm: Beats per minute; SDRR: Standard deviation of RRI; CVRR: Coefficient of variation of RRI; TP: Total power; VLFP: Very-low-frequency power; LFP: Low-frequency power; HFP: High-frequency power; nVLFP: Normalized VLFP; nLFP: Normalized LFP; nHFP: Normalized HFP; LHR: Low-/high-frequency power ratio; ms: Millisecond; nu: Normalized unit.

The HR of both genders at 520 and 1080 MASL were significantly smaller than that at 30 MASL, while the mRRI, SD_{RR} and TP of both genders at 520 and 1080 MASL were all significantly greater than those at 30 MASL (Table 6). Though there were no significant differences in CV_{RR} and VLFP between genders at 30 MASL, these 2 HRV measures of female subjects were increased gradually and significantly when the subjects were ascended to a higher altitude. This phenomenon was not observed in the male subjects. All HRV measures of both genders at 1080 MASL were not significantly different from those at 520 MASL.

Discussion

This study examined how the autonomic nervous modulation of healthy subjects was influenced by altitude in low-altitude mountain tourism. Our research was different from previous studies performed for trekkers at higher altitudes in that the confounding factors, such as oxygen consumption, physical exertion, water and food intake, etc., were excluded or minimized. Therefore, the major changes in HRV measures observed in this study might be caused predominantly by the change in altitude during tourism. It was demonstrated that travelling in the low-altitude mountain area could result in the change in the autonomic nervous modulation of healthy sea-level residents. As

altitude was increased from 30 MASL to 520 MASL and 1080 MASL, the HR and BP were decreased, while the overall HRV (SD_{RR}, CV_{RR} and TP), the Vagal Modulation (HFP) and sympatho-vagal modulation (LFP) were increased. The increase in overall HRV reflected the enhancement of mixed sympathetic and vagal modulations [22]. The overall HRV has strong prognostic value in adverse cardiovascular events [23]. The finding of increase in overall HRV in the low-altitude area in this study is in accordance with the general notion of feeling relaxed and comfortable during low-altitude tourism, because the sensation of comfort and relaxation is often correlated with increased vagal modulation [7,13]. Thus, mountain tourism in low-altitude area within 1080 MASL may have good effect on human physiological fitness of the sea-level residents in terms of autonomic nervous modulation and blood pressure regulation.

In previous studies about the HRV in the mountains higher than 1500 MASL, the HR was increased and the HRV was decreased when the altitude was increased [24]. The major contributing factor for the decrease in HRV was shown to be the hypoxia induced by low partial pressure oxygen at altitudes above 1500 meters [25]. In contrast, this study in low-altitude tourism showed that many HRV measures were increased as altitude was increased. The main reason for our favourable results in low-altitude tourism as compared with higher altitude tourism might be that there is less hypoxia effect in low-altitude area because the partial pressure of oxygen is relatively preserved when the attitude is below 1500 MASL.

Comparison of the changes in BP and HRV measures among 3 altitude changes revealed that the main changes in HRV measures occurred in the ascent from 30 to 520 MASL, rather than the ascent from 520 to 1080 MASL (Figure 1). Furthermore, the SBP, MABP, mRRI, SD_{RR}, CV_{RR}, TP, VLFP, and HFP reached their peak values at around 520 MASL, rather than at 1080 MASL (Table 1). It seems that the greatest change in BP and HRV measures occurred at around 520 MASL which meets the altitudes categories between “near sea-level” (0–500 MASL) and “low-altitude” (500–2000 MASL) [4]. Further studies may be necessary in the future to find out the best altitude that is easily accessible to the public while giving rise to the greatest decrease in BP and the greatest increase in HRV measures.

Many studies have reported that HRV correlated significantly and negatively with age [26]. In adult, both time and frequency domain HRV measures including SD_{RR}, Root Mean Squared Successive Difference (rMSSD), pNN50, VLF, LF and HF decline with age [27]. In this study, we found similarly that age correlated significantly and negatively with SDRR, CVRR, TP, LFP and HFP whatever the altitude was. In addition, though the age has positive correlation with nVFP, it has no correlation with nLFP, nHFP and LHR. This finding suggested that the renin-angiotensin-aldosterone modulation and thermoregulation of the subject increased with increasing age, but the vagal and sympathetic modulation of the subject was not affected by age. In this study we found that the SBP, MABP and PP were all significantly decreased when the subjects ascended from 30 MASL to a higher altitude in the old group, but not in the young group. This finding suggested that the blood pressures of the old subjects can be decreased to more extent than the young subjects by ascending to a higher altitude in the low-altitude mountain area. Thus, travel in the low-altitude mountain area might have some anti-hypertensive effects in the older subjects, but not in the young subjects.

Gender-related difference in HRV has been reported by many researches. Huikuri et al. [28] reported that the nLFP and LHR of male subjects were larger than those of female subjects. Antelmi et al. [27] reported that women had higher HFP, rMSSD, and pNN50, while men had higher VLFP, LFP, and SD_{RR}. In this study, no difference in HRV was observed between different genders at 30 and 1080 MASL. However, at altitude 520 MASL the SD_{RR}, CV_{RR}, TP and LFP in male subjects were significantly higher than those of the female subjects. Our results suggested that different genders reacted somewhat differently to altitude in terms of autonomic nerve modulation. The male subjects had higher overall HRV at 520 MASL, especially the low-frequency components, as compared with those of the female ones.

There were no significant differences in CV_{RR} and VLFP between genders at 30 MASL in this study. When the subjects were ascended to a higher altitude, the CV_{RR} and VLFP of the female subjects were increased gradually and significantly, while the CV_{RR} and VLFP of the male subjects remained unchanged. This difference in the response of CV_{RR} and VLFP to altitude change between genders might be related to the differences in the body composition and the structure of cardiovascular trees between male and female subjects, because the VLFP is an indicator of renin-angiotensin-aldosterone modulation and vagal withdrawal, and the CVRR is an index of overall vagal modulation, and because the blood pressures of the female subjects were lower than those of the male subjects at 30 MASL.

In addition to altitude, environmental variables might also be the factors that could affect the autonomic nerve modulation of the subjects in real wilderness. For instance, the ambient temperature might influence the VLF component which was known to be related to thermoregulation [21]. The VLFP and DBP were increased in cold room, and that the HR and nLFP were increased while the nHFP and SBP were decreased in hot room [29]. In this study, though the humidity at 1080 MASL was significantly lower than that at 30 and 520 MASL, no relationship was found between the relative humidity and HRV measures at altitude 1080 MASL. However, we found that the nVLFP in the old group was significantly increased at 520 and 1080 MASL, though at 30 MASL it was not significantly different between the young and old groups. In addition, though the nHFP was not significantly different between the young and old groups at 30 MASL, it was significantly increased at 520 MASL in the old group. Since the nVLFP is often used as the index of renin-angiotensin-aldosterone modulation and vagal withdrawal [19,20], or the index of thermoregulation [21], and the nHFP is often used as the index of vagal modulation, the increase in nVLFP and the decrease in nHFP at higher altitudes in the old group suggested that the renin-angiotensin-aldosterone modulation, vagal withdrawal and thermoregulation in the old subjects were more likely to be affected by the altitude than the young subjects. Environmental factors related to altitude changes might have played some role in this phenomenon.

Limitations

Firstly, the study subjects stayed at each altitude for about 30 minutes, and the study itinerary was totally about 3 hours for each subject. It may not be appropriate to draw definite conclusions from the results obtained from so short a stay at each altitude, as compared with some tourism that lasted for more than one day [30]. Secondly, in real wilderness, environmental factors that can affect the autonomic nervous modulation include not only altitude, temperature and humidity, but also smell, noise, scenes, constituents of air, etc. The effects of the later factors on the autonomic nervous modulation were not taken into account in this study. Thirdly, randomization with respect to the 3 altitudes in the mountain area is not possible because

the 3 altitudes in the mountain area are not on the same footing. For people living in the plain, the natural sequence of experimentation inevitably starts from 30 MASL and then goes to 520 MASL and 1080 MASL. This sequential procedure starting with 30 MASL and followed by 520 MASL and 1080 MASL respectively is similar to that of a control state followed by subsequent interventional states. It is not possible to start from either 520 MASL or 1080 MASL without the help of a helicopter, and then to other altitudes without interference from the condition of the previous altitude and the transportation process. Thus, randomization is not achievable in such situation. Finally, the study subjects included were healthy people; the effects of altitude on the autonomic nervous modulation of patients with various kinds of diseases were not evaluated. Further studies may be needed to assess in more details the effects of altitude and many environmental factors on the autonomic nervous modulation of both healthy subjects and patients with different kinds of diseases in wilderness.

Conclusion

Low-altitude mountain tourism, a popular worldwide outdoor activity, can lead to a decrease in HR and BP, and an increase in overall HRV within the altitude range of 1080 MASL. The greatest decrease in HR and BP and the greatest increase in overall HRV occur at around 520 MASL. The autonomic nervous modulation and blood pressure regulation of different genders respond slightly differently to altitude changes. Travel in the low-altitude mountain area may be good for physiological fitness in terms of automatic nervous modulation and blood pressure regulation, especially in the older people. The results of this study may provide clue to the answer of the common experience that people often feel comfort and relaxation when they travel to low-altitude mountain area. Whether a longer stay at low-altitude mountain area is really good for health remains to be explored by future studies.

Acknowledgements

This study was supported by the grant VGHUST96-P1-06 of the Joint Research Program of Taipei Veterans General Hospital and University System of Taiwan, Taiwan, and the grant V99C1-106 of Taipei Veterans General Hospital, Taipei, Taiwan.

References

1. Hackett PH, Roach RC (2001) High-altitude illness. N Engl J Med 345: 107-114.
2. Clarke C (2006) Acute mountain sickness: medical problems associated with acute and subacute exposure to hypobaric hypoxia. Postgrad Med J 82: 748-753.
3. Saito S, Tanobe K, Yamada M, Nishihara F (2005). Relationship between arterial oxygen saturation and heart rate variability at high altitudes. Am J Emerg Med 23: 8-12.
4. Bartsch P, Saltin B (2008) General introduction to altitude adaptation and mountain sickness. Scand J Med Sci Sports Suppl 1: 1-10.
5. Schobersberger W, Leichtfried V, Mueck-Weymann M, Humpeler E (2010) Austrian Moderate Altitude Studies (AMAS) (2010) Benefits of exposure to moderate altitudes (1,500-2,500 m). Sleep Breath 14: 201-207.
6. De Meersman RE, Reisman SS, Daum M, Zorowitz R, Leifer M, et al. (1995) Influence of respiration on metabolic, hemodynamic, psychometric, and R-R interval power spectral parameters. Am J Physiol 269: H1437-440.
7. Chuang CY, Han WR, Li PC, Young ST (2010) Effects of music therapy on subjective sensations and heart rate variability in treated cancer survivors: a pilot study. Complement Ther Med 18: 224-226.
8. Chen WL, Kuo CD (2007) Characteristics of heart rate variability can predict impending septic shock in emergency department patients with sepsis. Acad Emerg Med 14: 392-397.
9. Kleiger RE, Stein PK, Bigger JT Jr (2005) Heart rate variability: measurement and clinical utility. Ann Noninvasive Electrocardiol 10: 88-101.
10. Kuo CD, Chen GY, Wang YY, Hung MJ, Yang JL (2003) Characterization and quantification of the return map of RR intervals by Pearson coefficient in patients with acute myocardial infarction. Auton Neurosci 105: 145-152.
11. Hainsworth R, Drinkhill MJ, Rivera-Chira M (2007) The autonomic nervous system at high altitude. Clin Auton Res 17: 13-19.
12. Sizlan A, Ogur R, Ozer M, Irmak MK (2008) Blood pressure changes in young male subjects exposed to a median altitude. Clin Auton Res 18: 84-89.
13. Strauss-Blasche G, Riedmann B, Schobersberger W, Ekmekcioglu C, Riedmann G, et al. (2004) Vacation at moderate and low altitude improves perceived health in individuals with metabolic syndrome. J Travel Med 11: 300-304.
14. Hu J, Jiang X, Li N, Yu X, Perkovic V, et al (2009) Effects of salt substitute on pulse wave analysis among individuals at high cardiovascular risk in rural China: a randomized controlled trial. Hypertens Res 32: 282-288.
15. Schettini C, Bianchi M, Nieto F, Sandoya E, Senra H (1999) Ambulatory blood pressure: normality and comparison with other measurements: Hypertension Working Group. Hypertension 34: 818-825.
16. Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, et al (1985) Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 248: H151-153.
17. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 93: 1043-1065.
18. Saul JP, Arai Y, Berger RD, Lilly LS, Colucci WS, et al. (1988) Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. Am J Cardiol 61: 1292-1299.
19. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, et al. (1981) Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 213: 220-222.
20. Taylor JA, Carr DL, Myers CW, Eckberg DL (1998) Mechanisms underlying very-low-frequency RR-interval oscillations in humans. Circulation 98: 547-555.
21. K'Itney RI (1974) The analysis and simulation of the human thermoregulatory control system. Med Biol Eng 12: 57-65.
22. Stein PK, Ehsani AA, Domitrovich PP, Kleiger RE, Rottman JN (1999) Effect of exercise training on heart rate variability in healthy older adults. Am Heart J 138: 567-576.
23. Aronson D, Mittleman MA, Burger AJ (2004) Measures of heart period variability as predictors of mortality in hospitalized patients with decompensated congestive heart failure. Am J Cardiol 93: 59-63.
24. Huang HH, Tseng CY, Fan JS, Yen DH, Kao WF, et al. (2010) Alternations of heart rate variability at lower altitude in the predication of trekkers with acute mountain sickness at high altitude. Clin J Sport Med 20: 58-63.
25. Chen YC, Lin FC, Shiao GM, Chang SC (2008) Effect of rapid ascent to high altitude on autonomic cardiovascular modulation. Am J Med Sci 336: 248-253.
26. Kochiadakis GE, Papadimitriou EA, Marketou ME, Chrysostomakis SI, Simantirakis EN, et al. (2004) Autonomic nervous system changes in vasovagal syncope: is there any difference between young and older patients? Pacing Clin Electrophysiol 27: 1371-1377.
27. Antelmi I, de Paula RS, Shinzato AR, Peres CA, Mansur AJ, et al. (2004) Influence of age, gender, body mass index, and functional capacity on

heart rate variability in a cohort of subjects without heart disease. Am J Cardiol 93: 381-385.

28. Huikuri HV, Pikkujamsa SM, Airaksinen KE, Ikaheimo MJ, Rantala AO, et al. (1996) Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. Circulation 94: 122-125.

29. Sollers JJ 3rd, Sanford TA, Nabors-Oberg R, Anderson CA, Thayer JF (2002) Examining changes in HRV in response to varying ambient temperature. IEEE Eng Med Biol Mag 21: 30-34.

30. Yamasaki Y, Kodama M, Matsuhisa M, Kishimoto M, Ozaki H, et al. (1996) Diurnal heart rate variability in healthy subjects: effects of aging and sex difference. Am J Physiol 271: H303-310.