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ORIGINAL ARTICLE

The usefulness of prophylactic use of acetazolamide in subjects with acute mountain sickness

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Abstract

Background: The mechanisms of acetazolamide (ACZ) in the prophylaxis of acute mountain sickness (AMS) remain unclear. This study evaluated the changes in physiological variables of sleep and heart rate variability (HRV) in subjects with earlier history of AMS who underwent prophylactic treatment of ACZ.

Methods: Nonacclimatized healthy subjects were transported using a bus from 555 m to 3150 m within 3 hours. Polysomnography (PSG) was performed 3 days before ascent (T0), for two consecutive nights at 3150 m (T1 and T2), and 2 days after descent (T3). HRV was measured before sleep and after awakening from T0 to T3. AMS was diagnosed using a self-reported Lake Louise score questionnaire. Subjects found confirmed to have AMS were enrolled in this study. The physiological variables and HRV were compared in AMS subjects without (control group) and with prophylactic ACZ (prophylactic ACZ group).

Results: Thirteen AMS subjects were enrolled. The PSG results were analyzed in eight and HRV were analyzed in nine of the 13 subjects. The prophylactic use of ACZ in the subjects with a history of AMS significantly improved sleep efficiency ($p = 0.012$) and awakening percentages ($p = 0.017$) at T1, significantly higher levels of arterial oxygen saturation (SaO_2) and lower values of partial pressure end-tidal carbon dioxide tension ($P_{ET}CO_2$) at four time points. Furthermore, they had a higher rapid eye movement sleep percentage ($p = 0.05$) at T2. Prophylactic ACZ treatment significantly increased the normalized unit of high frequency at T1 after awakening ($p = 0.028$).

Conclusion: Significantly higher quality of sleep, higher SaO_2 during sleep, and lower $P_{ET}CO_2$ at high altitude were found in the subjects with a history of AMS using prophylactic ACZ before rapid ascent. ACZ may accelerate the acclimatization process for rapid ascents to high altitudes by increasing parasympathetic tone based on HRV analyses.

Keywords: Acetazolamide; Acute mountain sickness; Heart rate variability; Polysomnography

1. INTRODUCTION

Acute mountain sickness (AMS) is the commonest high-altitude illnesses in nonacclimatized persons arriving at high altitudes. Rapid ascent to altitude above 2500 m may rapidly reduce the arterial oxygen saturation (SaO_2) because of the hypobaric hypoxic environment and may induce pathological disorders, such as AMS.[1,2] The AMS prevalence in Taiwan was 36% at an altitude of 3952 m;[3] 22% at an altitude of 1850–2750 m in Summit County, Colorado, United States,[4] and 42% at an altitude of 3000 m.[5]

Individuals who climb higher than 2500 m may experience worsening symptoms. Additionally, they may experience clouding of consciousness, unsteadiness when walking, and difficulty breathing. If left untreated, cases of high-altitude pulmonary edema or high-altitude cerebral edema are often fatal. The major determinants of AMS are the rate of ascent, the altitude reached, sleeping altitude, and individual genetic susceptibility.[6,7]

Our earlier study[8] showed that subjects with AMS had lower sleep efficiency, higher awakening percentages, lower central apnea index, longer latency to rapid eye movement (REM), and significantly lower percentages of REM sleep on the first night (T1) at an altitude of 3150 m. Another study by our team[9] showed the effects of rapid ascent on heart rate variability (HRV) of individuals with and without AMS. After rapid ascent, subjects with AMS exhibited no sympathetic excitement, but depressed cardiac parasympathetic modulation. Accordingly, changes in cardiac sympathetic and parasympathetic modulation might play a key role in acclimatization to acute hypobaric hypoxia and/or development of AMS.

Acetazolamide (ACZ), a carbonic anhydrase (CA) inhibitor, is a medication that is commonly used to ameliorate AMS.[10] Metabolic acidosis, which occurs with ACZ, is one of the major stimulant effects on the respiratory system during awake and sleep periods at high altitudes to improve arterial oxygen tension (PaO_2) and reduce arterial carbon dioxide tension ($PaCO_2$).[11] Therefore, we investigated the effect of prophylactic use of ACZ on AMS and the changes in physiological variables on sleep and HRV in subjects with a history of AMS subjected to prophylactic treatment with ACZ.

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2. METHODS

2.1. Subjects

Adult volunteers with AMS in our earlier study on rapid ascents to high altitudes were eligible for enrolment in this study on the prophylactic use of ACZ. Subjects with severe medical disorders and contraindications to high-altitude exposure and traveling to altitudes above 2000 m in the 2 months before the study were excluded.

We excluded subjects who regularly used hypnotics or sedatives at bedtime and had adequate physical fitness (defined as subjects with sufficient mountaineering experience or who frequently traveled to altitudes exceeding 2000 m).

Subjects who were confirmed to have AMS in our previous study (control group) could participate in this study with prophylactic use of ACZ 250 mg tid 1 day before rapid ascent to high altitudes (prophylactic ACZ group).

2.2. Design

The study protocol (Figure 1) was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGH IRB No. 94-10-14A; 96-01-64A; 97-01-86A), and informed consent was obtained from each subjects. Beverages containing caffeine were prohibited for at least 24 hours before measurements. At high altitudes, activity of daily living and mountaineering were allowed during daytime. Subjects complaining of dyspnea were allowed to use supplemental oxygen, but their data were excluded for analysis.

2.3. Polysomnography

Polysomnography (PSG) parameters were measured four times in each subjects: three days before ascent (T0), the first two nights following rapid ascent to an altitude of 3150 m (T1 and T2), and 2 days after descent (T3).

PSG was performed using an Alice 4 (Healthdyne, Atlanta, Georgia, USA) by certified sleep technicians. A nasal pressure transducer (PTAF2; Pro-Tech, Woodinville, WA, USA) was used to detect minor changes in airflow and estimate hypopneas.[12]

PSG recordings were scored according to the standard criteria for the scoring of sleep stages and associated events by certified sleep technicians.[13–16] Sleep stages were scored in 30-s sequential epochs and analyzed manually through electroencephalography, electrooculography, and chin electromyography. Apnea was defined as a drop in the peak thermal sensor excursion of ≥90% of the baseline for ≥10 s. Hypopnea was defined as a drop in the nasal pressure signal of ≥30% of the baseline that lasted ≥10 s, resulting in a ≥4% decrease in SaO_2 from the pre-event baseline. Apnea–hypopnea index (AHI) was the number of apnea and hypopnea events recorded during the sleep study per hour of total sleep time (TST). Respiratory events could be assessed by measuring chest and abdominal wall movement that those were to demonstrate respiratory effort to distinguish between an obstructive sleep apnea with respiratory effort and central sleep apnea without respiratory effort. A pulse oximeter (for monitoring SaO_2, SpO_2) was used to record both the pulse and parameters associated with SpO_2, including mean and minimum SpO_2 and desaturation index (≥4% decrease in SpO_2, recorded during the study per hour of TST).

2.4. Partial pressure of end-tidal carbon dioxide

Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$; mmHg) was measured on the day of ascent (i.e., at sea level) and

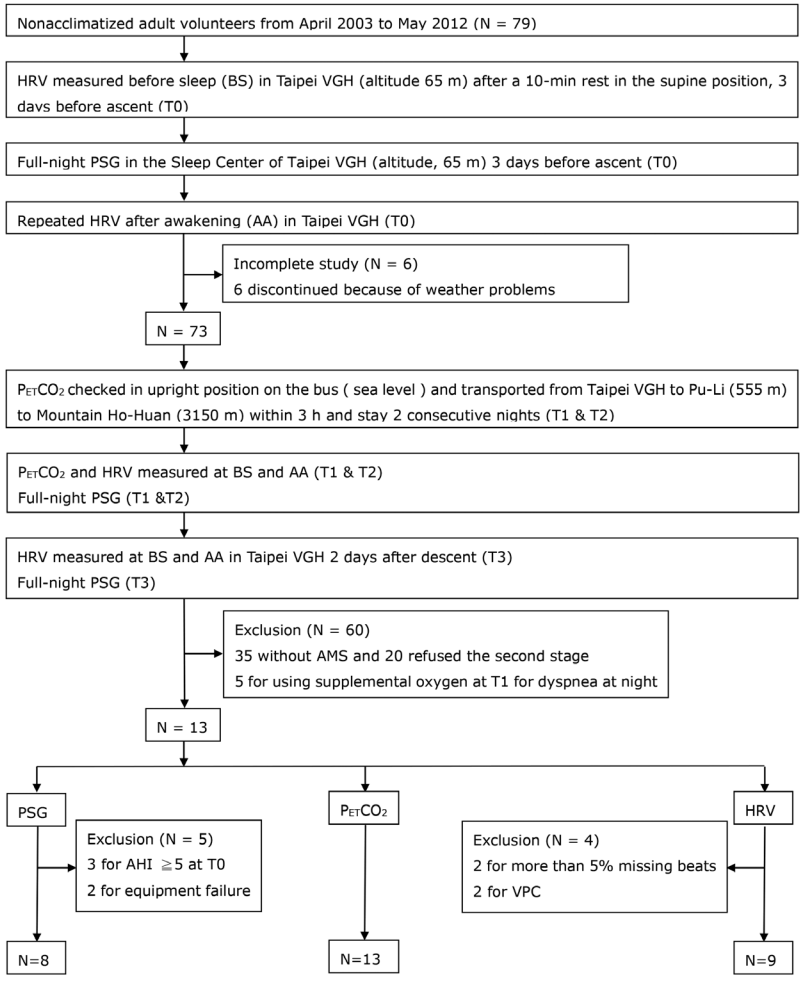

Fig. 1 Flowchart of study subjects and study protocol.

performed before sleep (BS) at night and after awakening (AA) on the next morning at high altitudes (T1 and T2) by using a tidal wave handheld capnography (Model 610; Novametrix Medical Systems, Inc., Wallingford, CT, USA). The subjects were tested in a seated position and were instructed to breath normally for 60 s through an airway adapter with a mouthpiece. The median value was recorded once the breathing pattern reached a steady state. Data on SpO_2 and pulse rate (PR) at awakening were obtained simultaneously.

2.5. Heart rate variability

Short-term HRV was measured at BS and AA using a handheld instrument (CheckMyHeart, DailyCare BioMedical Inc., Zhongli, Taiwan). After resting in a supine position for 10 min, 15-min electrocardiogram (ECG) was recorded in the same position at BS. Subjects were asked to relax (but not to fall asleep) and breathe naturally. On the subsequent morning, the subjects again underwent 15-min ECG at AA but before they got out of bed.

Autonomic cardiovascular function was evaluated through rate–rate interval (RRI) analysis by using built-in software. A 5-min ECG waveform was conducted and artifacts, large transients, or signal fluctuations were not included in the calculation of HRV was obtained to measure consecutive RRIs. Atrial and ventricular arrhythmias and sinus pauses were excluded; the consequent missing data were replaced with interpolated beats derived from the nearest valid data. If more than 5% of the beats were deleted, the data were excluded.

HRV data, including time and frequency domains, were analyzed in accordance with the HRV guidelines of the Task Force.[17] Time-domain measurements included the mean RRIs, standard deviation of all normal to normal (NN) intervals, the square root of the mean squares of differences of successive NN intervals (RMSSD), the number of interval difference of successive NN intervals more than 50 ms (NN50), the proportion derived by dividing NN50 by the total number of NN intervals (pNN50). Fast Fourier transform spectrum was used to analyze frequency domains as total power (TP: 0.01–0.4 Hz), very low frequency (VLF: 0.01–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), and high frequency (HF: 0.15–0.4 Hz). The normalized unit of LF (LFnu) and normalized unit of high frequency (HFnu) were calculated, as LF/(TP – VLF) × 100 and HF/(TP –VLF) × 100, respectively.

2.6. Evaluation of AMS

Self-reported Lake Louise scores (LLSs) were used to diagnose AMS. Subjects were asked to complete the LLS questionnaire before sleeping and AA, and the highest score during the stay at high altitudes was considered the final score. Subjects were diagnosed with AMS if their LLSs were ≥3 in the presence of a headache with one or more of the following: gastrointestinal symptoms (nausea, anorexia, or vomiting), dizziness, difficulty sleeping, and fatigue or weakness.[18,19]

2.7. Statistical data analysis

Data reported were mean ± standard error of the mean (SEM) in the HRV variables, and mean ± standard derivation (SD) in the other variables. Nonparametric tests were used to analyze the variables because the dispersion of the data was wide. Differences between the subjects with AMS who did not use ACZ for prophylaxis and the subjects who did use ACZ for prophylaxis were assessed using the Wilcoxon signed-rank test. For intragroup comparisons, the differences in HRV and $P_{ET}CO_2$ between BS and AA were evaluated using the Wilcoxon signed-rank test. The differences in PSG and HRV parameters over the four time points were examined through pairwise comparisons by using the Wilcoxon signed-rank test and Bonferroni correction. Statistical analyses were conducted using the PASW (Predictive Analytics Suite Workstation) 18.0 statistical software package (SPSS Inc., Chicago, USA). Significance was set at $p < 0.05$ (2-tailed) except for variables applicable to the Bonferroni correction. For intragroup comparisons, significance was set at $p < 0.0083$ (0.05 ÷ 6).

3. RESULTS

3.1. Subject characteristics

Thirteen AMS subjects were included in the analysis (three men and 10 women; age range: 23–60 years [mean ± SD, 45.2 ± 12.4 years]). AMS was persistent in 1 (female) of the 13 (7.7%) subjects after using ACZ for prophylaxis. However, the severity was reduced remarkably. The time between the subjects participated the study diagnosed to have AMS and the study on the prophylactic use of ACZ were separated in time by 4–53 months (mean ± SD, 17.2 ± 14.0 months).

3.2. The effect of prophylactic ACZ on PSG parameters in subjects with AMS

Three subjects with AHI ≥ 5 at T0 and two subjects who experienced equipment failure were excluded. Ultimately, eight subjects were included in the PSG analysis.

The serial changes in sleep architecture in eight subjects with AMS indicated that the subjects with prophylactic use of ACZ exhibited higher-quality sleep. Compared with the data without ACZ, the data with ACZ exhibited higher sleep efficiency (73.0 ± 14.5 vs 85.8 ± 8.2, $p = 0.012$) and lower awakening percentages (24.1 ± 14.6 vs 11.1 ± 6.6, $p = 0.017$) at T1. Moreover, greater REM sleep percentages (11.3 ± 5.9 vs 15.5 ± 6.8, $p = 0.05$) at T2 was found in the subjects with prophylactic ACZ. Shortening of the latency to REM sleep measured at T1 was found in the subjects with prophylactic use of ACZ.

Over time, changes in respiratory events and oxygenation-related parameters were observed in eight subjects with AMS. The use of prophylactic ACZ improved SaO_2. In addition, significantly higher mean SpO_2 (80.5 ± 6.4 vs 86.9 ± 2.6, $p = 0.025$) and significantly higher minimum SpO_2 (71.5 ± 8.7 vs 78.5 ± 3.3, $p = 0.027$) at T1 were found in the subjects with prophylactic ACZ. At a high altitude (T1 and T2), the values for AHI, hypopnea index, and desaturation index were slightly higher than those at sea level (T0 and T3).

3.3. The effect of prophylactic ACZ on $P_{ET}CO_2$ in subjects with AMS

All 13 subjects were included in the $P_{ET}CO_2$ analysis. $P_{ET}CO_2$ was measured at five time points: sea level, T1 BS, T1 AA, T2 BS, and T2 AA. The $P_{ET}CO_2$, SpO_2, and PR values were comparable despite the prophylactic use of ACZ (Figure 2). Stepwise decreases were observed in the level of $P_{ET}CO_2$ from sea level to T2 AA. Prophylactic use of ACZ could significantly decrease the levels of $P_{ET}CO_2$ for all recorded times, and significantly increase the levels of SpO_2 at four time points, except for T1 AA. Moreover, prophylactic use of ACZ might lower the levels of PR slightly.

3.4. The effect of prophylactic ACZ on HRV parameters in subjects with AMS

Two subjects with more than 5% missing beats and two subjects recorded with ventricular premature contraction were excluded. Ultimately, nine subjects were included in the HRV analysis.

Almost all parameters indicative of parasympathetic tone, including RMSSD, NN50, pNN50, and HF, increased at T1 AA rather than T1 BS in subjects with prophylactic use of ACZ (Figure 3). In addition, the subjects with prophylactic use of ACZ had significantly higher HFnu at T1 AA ($p = 0.028$), RMSSD ($p = 0.015$), and pNN50 ($p = 0.021$), and the LF/HF ratio ($p = 0.038$) significantly decreased at T3 AA.

At a high altitude, the AA HFnu of parasympathetic tone significantly decreased compared with that BS; however, the LF/HF ratio for sympathovagal balance increased significantly. Throughout T0–T3 AA, the subjects with prophylactic use of

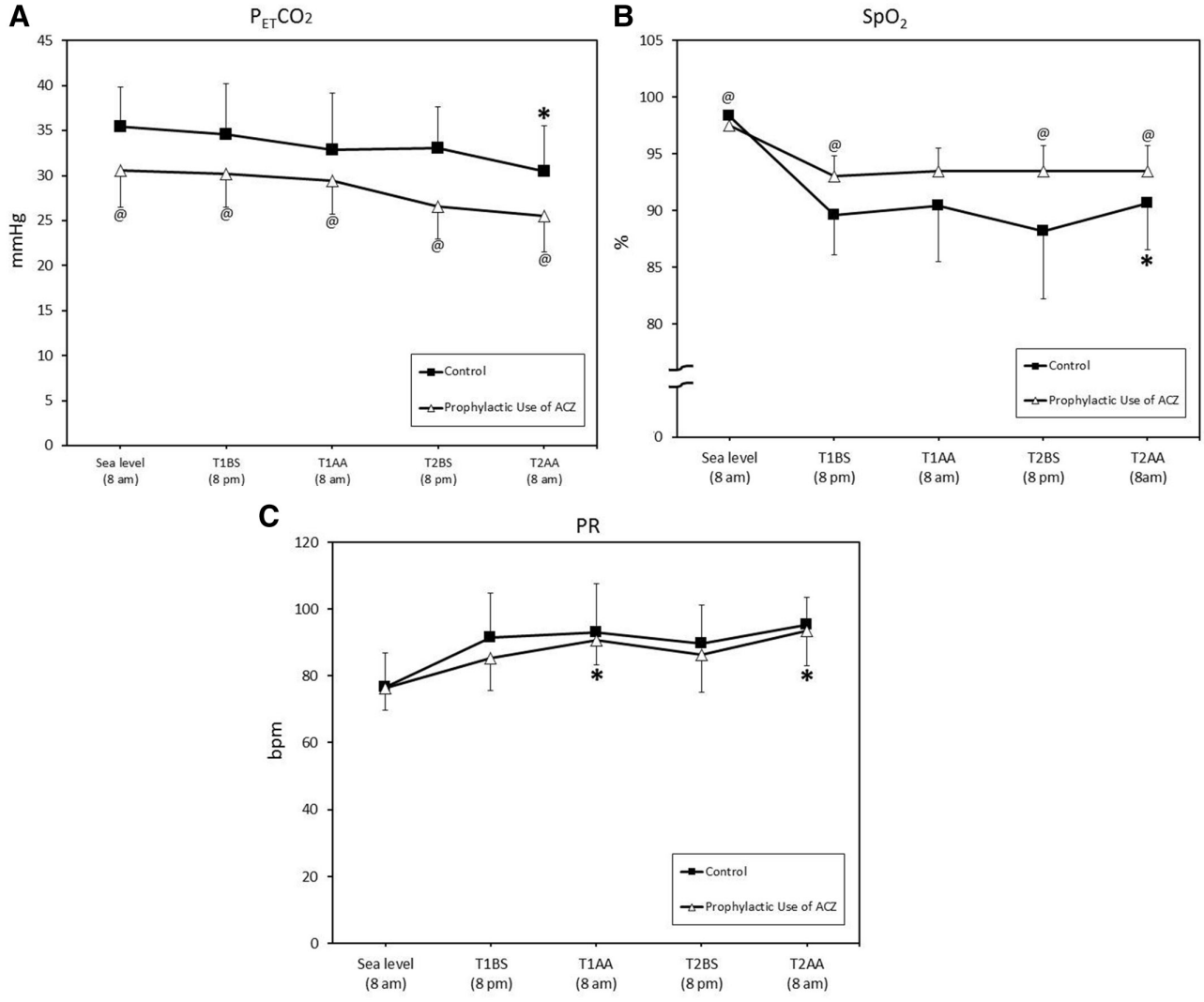

Fig. 2 End-tidal PCO_2 ($P_{ET}CO_2$, A), arterial oxygen saturation (SpO_2, B), and pulse rate (PR, C) measured at different time points in the subjects with acute mountain sickness (AMS) with and without prophylactic use of acetazolamide (ACZ). @ indicated comparisons between groups: $p < 0.05$ with vs without ACZ; * indicated comparisons between groups: *$p < 0.05$ BS vs AA.

ACZ had consistently higher levels of all time-domain parameters and all spectral segments (namely TP, VLF, LF, and HF) than at T0–T3 BS. The AA HFnu were lower than the BS HFnu, with significant differences observed at T1 (46.0 ± 7.6 vs 29.9 ± 5.8, $p = 0.021$) and T2 (40.8 ± 6.6 vs 18.8 ± 4.0, $p = 0.008$); moreover, the levels of LFnu were lower at T2 AA than at T2 BS. At sea level (T0), the AA LF/HF ratios were slightly lower than the BS LF/HF ratios. However, at T1 (1.1 ± 0.3 vs 2.1 ± 0.6, $p = 0.038$) and T2 (1.4 ± 0.6 vs 2.9 ± 0.9, $p = 0.036$), the AA LF/HF ratios were significantly higher than the BS LF/HF ratios.

BS, the data of LFnu of sympathetic tone and LF/HF ratio nonsignificantly decreased at T1 more than those did at T0 but increased at T2 more than those did at T1. By contrast, the data of HFnu of parasympathetic tone slightly increased at T1 more than those did at T0 but decreased at T2 more than those did at T1. Stepwise decreasing trends were noted for all time-domain parameters and all spectral segments from T0 to T2 BS. At a high altitude BS, the data of LFnu and LF/HF ratio decreased, but the data of HFnu increased when compared with those at T0 BS. By contrast, both the data of LFnu and LF/HF ratio were slightly lower, but the HFnu were higher at T1 BS than those at T2 BS. No significant differences were observed in the levels of all time- and frequency-domain parameters at T0 and T3 BS.

Similarly, stepwise decreases were noted in the levels of all time-domain parameters, all spectral segments, and HFnu from T0 to T2 AA. The AA LFnu increased at a high altitude, and the values remained slightly higher at T1 AA than at T2 AA. The LF/HF ratio gradually increased from T0 to T2 AA. All HRV values were similar between T0 and T3 AA.

3.5. Side effects of ACZ in subjects with AMS

We estimated the side effects from ACZ in 13 subjects with prophylactic use of ACZ. The side effects of ACZ were noted including numbness, gastrointestinal discomfort, dizziness, leg edema, and headache. However, the side-effects were uncommon, mild, and well tolerated by the subjects.

4. DISCUSSION

To the best of our knowledge, this is the first pilot study to evaluate the effect of rapid ascent to a high altitude for two consecutive days on sleep and HRV changes and to compare the clinical relevance of prophylactic use of ACZ in particular in those with a history of AMS using the same protocol of rapid ascent to a high altitude. We assessed sleep quality through full-night PSG, so that we could understand more about the sleep architecture and respiratory events. We demonstrated that subjects with a history of AMS treated with prophylactic ACZ could improve sleep quality. They had higher sleep efficiency, lower awakening percentages, higher mean SpO_2, and higher minimum SpO_2 at T1.

At T2, they had higher percentages of REM sleep. Furthermore, the variables indicative of parasympathetic activity based on an analysis of HRV (NN50, pNN50, and HF) increased at T1 AA compared with those at T1 BS. By contrast, sympathetic activity showed no significant change between T1 AA and T1 BS.

ACZ was confirmed to reduce symptoms of AMS and facilitate acclimatization.[20] However, the actual mechanisms remain unclear and require further investigations to elucidate. ACZ increases the excretion of bicarbonate in the proximal tubule of the kidney, resulting in metabolic acidosis and the balance of hyperventilation-induced respiratory alkalosis.[6,10,21] ACZ stimulates ventilation, improves oxygenation, and accelerates the body's acclimatization process. A study reported that the differences in mean AMS scores over time exhibited a statistically significant decline in the ACZ group versus the placebo group, and ACZ effectively reduced the symptoms of AMS over a 24-h period after arrival at 3630 m.[22]

ACZ reduced the incidence and severity of sleep-disorder breathing and was associated with improvements in SaO_2, resulting in the enhancement of sleep quality.[23,24] In this study, the subjects with an AHI of ≥5 were excluded. Notably, ACZ still benefited sleep quality in subjects with a history of AMS without sleep-disorder breathing. Our results indicated that prophylactic use of ACZ could significantly improve mean and minimum SpO_2 in subjects with a history of AMS on the first night at a high altitude of 3150 m. Furthermore, the subjects with a history of AMS who were subjected to prophylactic use of ACZ had significantly higher sleep efficiency, lower awakening percentages, and more REM sleep. Our previous study[8] indicated that REM sleep delay and reduction was observed in subjects who were not acclimatized to acute hypobaric hypoxia. ACZ has been proven to reduce periodic breathing that is common in high-altitude sleep disturbance[25] and increase sleep quality.[24]

Teppema et al.[26] enrolled nine heathy volunteers to measure the effect of ACZ (250 mg orally every 8 h for 3 days) on the dynamic ventilator response to stepwise changes of $P_{ET}CO_2$. They showed that compared with placebo group, resting ventilation significantly increased from 12.22 ± 2.41 to 14.01 ± 1.85 L/min, resulting in a significant decrease in $P_{ET}CO_2$ from 40.0 ± 4.7 to 33.3 ± 3.5 mmHg in the ACZ group. Ventilation increased after

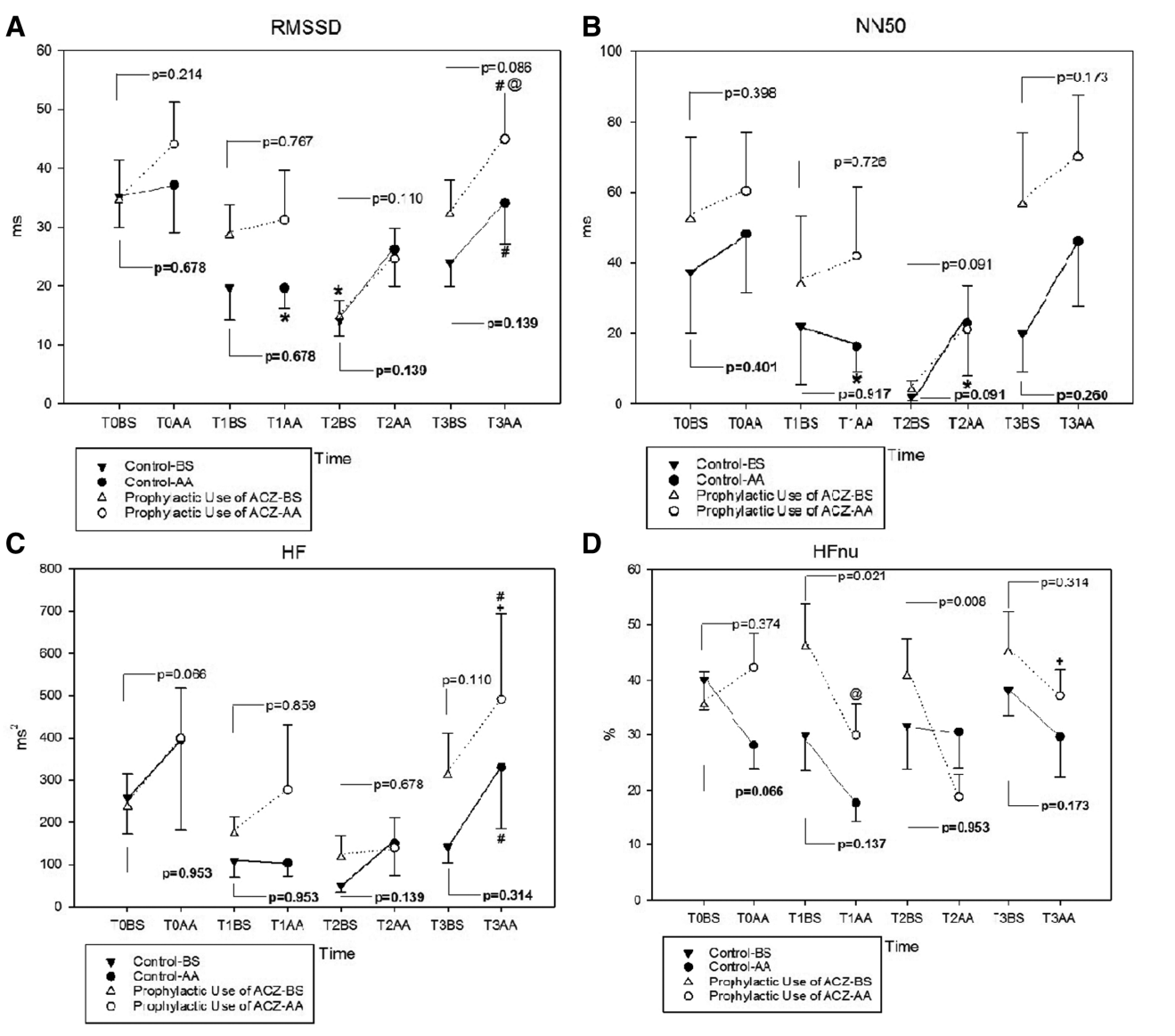

Fig. 3 The square root of the mean of the sum of the squares of differences between adjacent normal to normal (NN) intervals (RMSSD, A), the NN intervals differing by more than 50 ms (NN50, B), the NN50 count divided by total number of NN intervals (pNN50, C), high frequency (HF, D), the normalized unit of HF (HFnu, E), the normalized unit of LF (LFnu, F), and LF/HF (G) measured at different time points in the subjects with acute mountain sickness (AMS) with and without prophylactic use of acetazolamide (ACZ). @ indicated comparisons between groups: $p < 0.05$ with vs without ACZ. *, #, + indicated comparisons within groups: *$p < 0.0083$ vs T0; #$p < 0.0083$ vs T1; +$p < 0.0083$ vs T2.

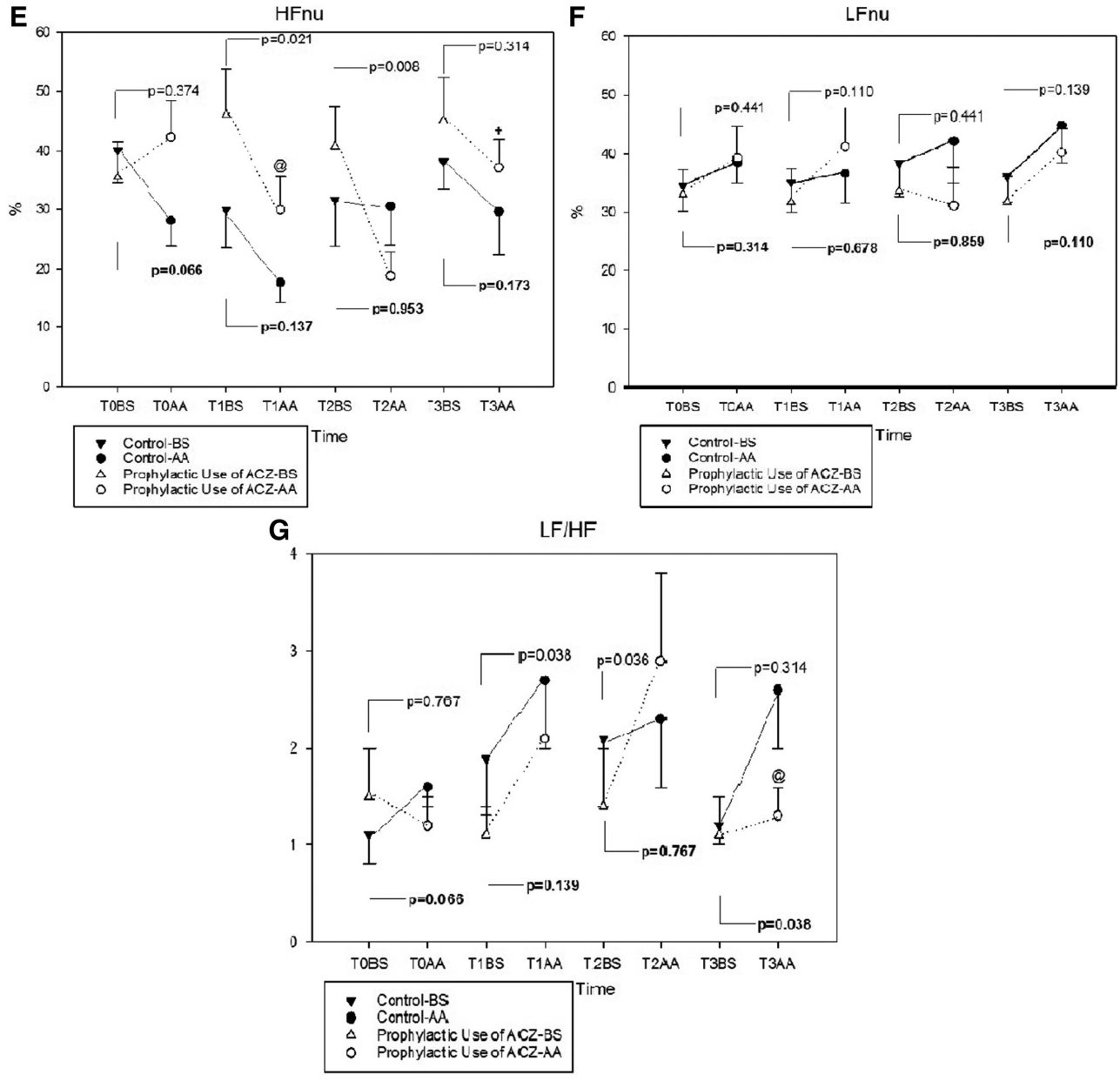

Fig. 3 (Continued)

the administration of ACZ, resulting in a decrease in $P_{ET}CO_2$ and an increase in $P_{ET}O_2$. In agreement with the previous study, our results indicated that $P_{ET}CO_2$ progressively decreased when the subjects rapidly ascended to a high altitude. The data of $P_{ET}CO2$ were significantly lower in subjects with a history of AMS with prophylactic use of ACZ than in the same subjects without the use of prophylactic ACZ (Figure 2).

In our previous report[9], we determined that parasympathetic activity (RMSSD, NN50, pNN50, and HFnu) decreased in subjects with a history of AMS but significantly increased in those without AMS on the first morning after a rapid ascent to a high altitude. Furthermore, in the present study, the prophylactic use of ACZ made the most marked distinction between the AMS subjects without (control group) and with (prophylactic ACZ group) prophylactic use of ACZ was the conflicting trends in the changes in parasympathetic tone after the first overnight sleep (Figure 3). In the current study, almost all parameters of parasympathetic activity increased at T1 AA compared with those at T1 BS in subjects with AMS who underwent prophylactic use of ACZ. The prophylactic use of ACZ in subjects with previous AMS tiled to increased parasympathetic activity. Some studies indicated that acclimatization of high altitude could be characterized by recovery of parasympathetic tone.[27–29] We found that prophylactic use of ACZ accelerated the high-altitude acclimatization process by increasing parasympathetic tone.

The limitations of this study were as follows. First, this study featured an unevenly distributed range of ages. Wang et al.[3] reported an AMS prevalence of 36% in trekkers at Jade Mountain, Taiwan; Bloch et al.[30] reported an AMS incidence of 37.5% in children ascending rapidly to 3450 m: the incidence of AMS in these children was almost identical to that of adults. Second, a sex imbalance was observed, with a female dominance. However, susceptibility to AMS does not differ between men and women.[31] Third, each AMS subjects without (control group) and with (prophylactic ACZ group) ACZ use was studied in a wide range of period 4–53 months (mean ± SD, 17.2 ± 14.0 months). Fourth, the sample size for subjects with below-average fitness was relatively small. Fifth, the severity of AMS might have been underestimated because five subjects with severe AMS who used supplemental oxygen were not included. However, the results

of this study provide valuable information about the effect of ACZ on the changes in sleep and HRV after rapid ascent to a high altitude and during the two consecutive days at the same altitude in the subjects with a history of AMS. Moreover, this study identified the differences between AMS subjects without (control group) and with (prophylactic ACZ group) prophylactic use of ACZ.

In conclusion, significantly higher quality of sleep, higher SpO_2 during sleep, and lower $P_{ET}CO_2$ at a high altitude were found in the subjects with a history of AMS using prophylactic use of ACZ before rapid ascent. ACZ may accelerate the acclimatization process for rapid ascents to high altitudes by increasing parasympathetic activity based on HRV analyses.

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REFERENCES

1. Bolmont B, Thullier F, Abraini JH. Relationships between mood states and performances in reaction time, psychomotor ability, and mental efficiency during a 31-day gradual decompression in a hypobaric chamber from sea level to 8848 m equivalent altitude. *Physiol Behav* 2000;**71**:469–76.
2. Yu J, Zeng Y, Chen G, Bian S, Qiu Y, Liu X, et al. Analysis of high-altitude syndrome and the underlying gene polymorphisms associated with acute mountain sickness after a rapid ascent to high-altitude. *Sci Rep* 2016;**6**:38323.
3. Wang SH, Chen YC, Kao WF, Lin YJ, Chen JC, Chiu TF, et al. Epidemiology of acute mountain sickness on Jade Mountain, Taiwan: an annual prospective observational study. *High Alt Med Biol* 2010;**11**:43–9.
4. Honigman B, Theis MK, Koziol-McLain J, Roach R, Yip R, Houston C, et al. Acute mountain sickness in a general tourist population at moderate altitudes. *Ann Intern Med* 1993;**118**:587–92.
5. Dean AG, Yip R, Hoffmann RE. High incidence of mild acute mountain sickness in conference attendees at 10,000 foot altitude. *J Wilderness Med* 1990;**1**:86–92.
6. West JB. The physiologic basis of high-altitude diseases. *Ann Intern Med* 2004;**141**:789–800.
7. Palmer BF. Physiology and pathophysiology with ascent to altitude. *Am J Med Sci* 2010;**340**:69–77.
8. Tseng CH, Lin FC, Chao HS, Tsai HC, Shiao GM, Chang SC. Impact of rapid ascent to high altitude on sleep. *Sleep Breath* 2015;**19**:819–26.
9. Yih ML, Lin FC, Chao HS, Tsai HC, Chang SC. Effects of rapid ascent on the heart rate variability of individuals with and without acute mountain sickness. *Eur J Appl Physiol* 2017;**117**:757–66.
10. Leaf DE, Goldfarb DS. Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. *J Appl Physiol* 2007;**102**:1313–22.
11. Swenson ER, Leatham KL, Roach RC, Schoene RB, Mills WJ Jr, Hackett PH. Renal carbonic anhydrase inhibition reduces high altitude sleep periodic breathing. *Respir Physiol* 1991;**86**:333–43.
12. Budhiraja R, Goodwin JL, Parthasarathy S, Quan SF. Comparison of nasal pressure transducer and thermistor for detection of respiratory events during polysomnography in children. *Sleep* 2005;**28**:1117–21.
13. Rechtschaffen A, Kales A. A Manual of Standardized Terminology. The techniques and scoring system for sleep stages of human subjects. *National Institutes of Health publication* 1968; no. **204**.
14. Atlas Task Force of American Sleep Disorders Association. EEG arousal: scoring rules and examples. *Sleep* 1992;**15**:174–84.
15. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999;**22**:667–89.
16. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. *J Clin Sleep Med* 2012;**8**:597–619.
17. Malik M. Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J* 1996;**17**:354–81.
18. Hackett PH, Roach RC. High-altitude illness. *N Engl J Med* 2001;**345**:107–14.
19. Imray C, Booth A, Wright A, Bradwell A. Acute altitude illnesses. *BMJ* 2011;**343**:d4943.
20. Luks AM, McIntosh SE, Grissom CK, Auerbach PS, Rodway GW, Schoene RB, et al. Wilderness Medical Society practice guidelines for the prevention and treatment of acute altitude illness: 2014 Update. *Wilderness Environ Med* 2014;**25**:S4–14.
21. Parise I. Travelling safely to places at high altitude – Understanding and preventing altitude illness. *Aust Fam Physician* 2017;**46**:380–4.
22. Carlsten C, Swenson ER, Ruoss S. A dose-response study of acetazolamide for acute mountain sickness prophylaxis in vacationing tourists at 12,000 feet (3630 m). *High Alt Med Biol* 2004;**5**:33–9.
23. Grissom CK, Roach RC, Sarnquist FH, Hackett PH. Acetazolamide in the treatment of acute mountain sickness: clinical efficacy and effect on gas exchange. *Ann Intern Med* 1992;**116**:461–5.
24. Fischer R, Lang SM, Leitl M, Thiere M, Steiner U, Huber RM. Theophylline and acetazolamide reduce sleep-disordered breathing at high altitude. *Eur Respir J* 2004;**23**:47–52.
25. Sutton JR, Houston CS, Mansell AL, McFadden MD, Hackett PM, Rigg JR, et al. Effect of acetazolamide on hypoxemia during sleep at high altitude. *N Engl J Med* 1979;**301**:1329–31.
26. Teppema LJ, Dahan A. Acetazolamide and breathing. Does a clinical dose alter peripheral and central CO(2) sensitivity? *Am J Respir Crit Care Med* 1999;**160**:1592–7.
27. Bhaumik G, Dass D, Bhattacharyya D, Sharma YK, Singh SB. Heart rate variabilty changes during first week of acclimatization to 3500 m altitude in Indian military personnel. *Indian J Physiol Pharmacol* 2013;**57**:16–22.
28. Cornolo J, Mollard P, Brugniaux JV, Robach P, Richalet JP. Autonomic control of the cardiovascular system during acclimatization to high altitude: effects of sildenafil. *J Appl Physiol* 2004;**97**:935–40.
29. Lanfranchi PA, Colombo R, Cremona G, Baderna P, Spagnolatti L, Mazzuero G, et al. Autonomic cardiovascular regulation in subjects with acute mountain sickness. *Am J Physiol Heart Circ Physiol* 2005;**289**:H2364–72.
30. Bloch J, Duplain H, Rimoldi SF, Stuber T, Kriemler S, Allemann Y, et al. Prevalence and time course of acute mountain sickness in older children and adolescents after rapid ascent to 3450 meters. *Pediatrics* 2009;**123**:1–5.
31. Hackett PH, Rennie D. The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet* 1976;**2**:1149–55.