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Blood pressure and left ventricular function changes in different ambulatory blood pressure patterns at high altitude

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Abstract

Acute high-altitude (HA) exposure induces physiological responses of the heart and blood pressure (BP). However, few studies have investigated the responses associated with dipper and non-dipper BP patterns. In this prospective study, 72 patients underwent echocardiography and 24-h ambulatory BP testing at sea level and HA. Patients were divided into dipper and non-dipper groups according to BP at sea level. Acute HA exposure elevated 24-h systolic and diastolic BP and increased BP variability, particularly in the morning. Moreover, acute exposure increased left ventricular torsion, end-systolic elastance, effective arterial elastance, and untwisting rate, but reduced peak early diastolic velocity/late diastolic velocity and peak early diastolic velocity/early diastolic velocity, implying enhanced left ventricular systolic function but impaired filling. Dippers showed pronounced increases in night-time BP, while non-dippers showed significant elevation in day-time BP, which blunted differences in nocturnal BP fall, and lowest night-time and evening BP. Dippers had higher global longitudinal strain, torsion, and untwisting rates after acute HA exposure. Variations in night-time systolic BP correlated with variations in torsion and global longitudinal strain. Our study firstly demonstrates BP and cardiac function variations during acute HA exposure in different BP patterns and BP increases in dippers at night, while non-dippers showed day-time increases. Furthermore, enhanced left ventricular torsion and global longitudinal strain are associated with BP changes. Non-dippers showed poor cardiac compensatory and maladaptive to acute HA exposure. However, the exact mechanisms involved need further illumination.

Renzheng Chen, Jie Yang, and Chuan Liu have contributed equally to this work.

1 | INTRODUCTION

High-altitude (HA) environments present a great challenge for humans as a result of continuous hypobaric hypoxia, cold temperatures, and high ultraviolet radiation levels. Tremendous progress has been made over the past decades in terms of the understanding of physiological adaptation to acute HA exposure, including the responses in arterial blood pressure (BP) and cardiac mechanisms.[1] Evidence has confirmed that both systolic and diastolic pressure increase after a few hours of HA exposure, particularly during the night, resulting in a reduction in nocturnal dipping, and this increase remains virtually unchanged over the following days.[2] The underlying mechanisms of this response may be associated with activation of the adrenergic system, increased arterial stiffness, endothelin release, and reduced vasodilatory responses.[3]

Arterial BP exhibits a diurnal rhythm that is characterized by low values during sleep, which regularly fall by approximately 15 percent. Several researchers have indicated that nocturnal decline in BP is blunted during acute HA exposure, especially in hypertensive patient.[4] A non-dipping BP pattern is usually regarded as a particularly harmful BP phenotype. People with this pattern have a higher risk of cardiovascular complications than individuals with a dipping circadian rhythm.[5,6] Therefore, BP patterns have been commonly used to assess the risk of cardiovascular events early and guide clinical prevention.[7] However, hardly any information is available on the BP characteristics after HA exposure in groups with different BP patterns. Moreover, the mechanism involved in the change in day-time and night-time BP during HA exposure is unclear.

Thus, in the present study, we recruited participants with dipping and non-dipping BP patterns and aimed to illuminate the characteristics of 24-h ambulatory blood pressure (ABP) during HA exposure in two cohorts. Given the cardiac mechanisms, echocardiography was performed to assess the mechanics and function of left ventricle and to account for the HA-induced BP responses in different BP patterns.

2 | METHODS

2.1 | Study population and ethical considerations

This study was a sub-study of a prospective high-altitude cohort study performed in 2019 in Chengdu, China. We recruited 91 patients from the ABP study, including 50 dipping pattern (DP) patients and 41 non-dipping pattern (non-DP) patients. The dipping pattern was identified by a reduction in nocturnal BP over 10%.[7] Exclusion criteria included the following: (1) cardiovascular diseases; (2) respiratory diseases and obstructive sleep apnea syndrome; (3) hematological disease; (4) HA exposure history in the last half year; (5) taking any oral medicine; and (6) ABP measurements performed for <80% of the whole day.[8] Informed consent was obtained from each patient, and all patients underwent a comprehensive medical examination before the expedition (at sea level [SL]; Chongzhou, 400 m). After arriving at HA (Litang, 4100 m above SL), all patients underwent their usual daily activities. Eighteen patients of DP and nine patients of non-DP were excluded because of the exclusion criteria and a lack of measurement data. Seventy-two patients at SL (Chengdu, 400 m, above SL) were included in this study. All patients were sea-level residents and aged from 19 to 60 years, including 43 males and 29 females. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the Human Ethics Committee, Xinqiao Hospital, Third Military Medical University (Identification code, 201907501). This study was registered at www.chictr.org.cn (ChiCTR-TRC-No.1900025728).

2.2 | 24-h ambulatory BP monitoring

24-h ABP monitoring was performed with an ABP measurement device (Spacelabs 90207), which was attached by well-trained cardiovascular physicians. The device cuff was applied to the non-dominant arm on a weekday morning and removed after 24 h. All participants were instructed to remain still during each measurement, avoid unusual physical activity, and comply with a standardized activity schedule, both at SL and at HA. Day-time was defined from 6:00 to 22:00 and nighttime from 22:00 to 6:00.[9] The recorders were programmed to measure BP every 30 min during day-time and at 60-min intervals during nighttime. Record data for the entire 24-h period and only recordings with at least 80% of the expected readings were rated as valid by pre-defined criteria.

2.3 | Calculation of the relevant BP parameters

Pre-waking BP was defined as the average BP during the 2 h just before wake-up time (4:00–6:00). Morning BP was defined as the average BP during the first 2 h after wake-up time (6:00–8:00). Evening BP was defined as the average BP during the 2 h before going to bed (22:00–24:00). The lowest BP was defined as the average BP of three readings of the lowest night-time reading. The morning blood pressure surge was calculated as the difference between morning BP and pre-waking SBP. Nocturnal BP fall was calculated as the value of nocturnal decline in systolic blood pressure (SBP) (day-time SBP − night-time SBP) × 100/day-time SBP.[10] We calculated the percentage fall in the nocturnal and morning BP surge in diastolic blood pressure (DBP) in the same way. Dipping ratio was the ratio of night-time SBP to day-time SBP. SBP decreases over 10% during sleep compared with day-time values was considered to represent a dipping pattern. In contrast, <10% was classified as a non-dipping pattern. The average real variability (ARV) of systolic BP was calculated using the following formula. Where K ranges from 1 to N and N denotes the number of valid BP measurements in the data corresponding to a given patient.[11] ARVs and ARVd denoted the ARV of SBP and DBP, respectively.

$$\frac{1}{N-1}\sum_{K=1}^{N-1}\left|BP_{k+1}-BP_k\right|$$

TABLE 1 Demographic parameters

Variables	All (n = 72)	Non-DP (n = 36)	DP (n = 36)	p Value
Age, years	26.99 ± 7.87	27.03 ± 6.40	26.94 ± 9.20	.351
BMI, kg/m^2	21.82 ± 2.17	22.10 ± 2.31	21.53 ± 2.00	.270
Sex (M/F)	45/27	21/15	24/12	.465
Alcohol (Y/N)	11/61	6/30	5/31	.743
Tobacco (Y/N)	28/44	13/23	15/21	.629
Race (Y/N)	1/71	0/36	1/35	1.000

Note: Values are presented as mean ± standard deviation.

Abbreviations: BMI, body mass index; DP, dipping pattern; F: female; N: non-Tibetan; Race, Y: Tibetan; Sex, M: male.

2.4 | Calculation of the relevant echocardiography parameters

The echocardiographic examination was performed using an ultrasound machine (CX50, Philips Ultrasound System) to acquire the data of the left ventricle (LV). Images were saved digitally for subsequent offline analysis using QLAB software (QLAB 10.5; Philips Healthcare). Measurements of LV dimensions and volumes were performed by a computerized analysis software system. Ejection fraction (EF) was calculated using the LV volume data. Mitral inflow from the tips level was analyzed for peak early diastolic velocity (*E*) and late diastolic velocity (*A*), and *E*/*A*. Mitral annulus early diastolic velocity (*e′*) was measured at the septal and lateral mitral annulus, and the *E*/*e′* ratio was calculated by the mean septal *E*/*e′* ratio and mean lateral *E*/*e′* ratio. Effective arterial elastance (Ea) and end-systolic elastance (Ees) were computed by SBP × 0.9/stroke volume and SBP × 0.9/end-systolic volume (ESV), while ventricular-arterial decoupling (VAC) was the ratio of Ea and Ees.[12] We used a two-dimensional ultrasound speckle tracking imaging technique to measure LV torsion, LV untwisting rate, and LV strain. The computer automatically selects suitable stable objects for tracking and then searches for them in the next frame using a sum of absolute differences algorithm. We defined LV torsion as the difference between the apical and basal angle during systole around the longitudinal LV axis relative to the starting position and the untwisting rate was the maximum untwisting velocity calculated by the angle during diastole.[13] The global longitudinal strain (GLS) was calculated by averaging all the values of the regional peak longitudinal strain obtained in two-chamber, three-chamber, and four-chamber apical views. The global circumferential strain (GCS) was assessed as the average of the three LV regional values measured in the parasternal short-axis view at the basal level. Measurements of three cardiac cycles were averaged.

2.5 | Reproducibility

Observer reliability of main echocardiographic measurements was assessed in 20 randomly selected patients. Interobserver variability was performed by two different physicians, and intraobserver variability was performed by the same physician at least 1 month apart. Both the interobserver and intraobserver variabilities were tested using the intraclass correlation coefficient (ICC). Corresponding results were listed in the Table S3.

2.6 | Statistical analysis

Continuous variables were presented as mean ± standard deviation. Differences in measurements at SL and HA were tested using a paired t test if they showed a normal distribution, and data that did not fit a normal distribution were analyzed with a Wilcoxon rank sum test. Differences in measurements between the non-DP group and DP group were tested with an independent-samples *T*-test and Mann–Whitney *U*-test. Categorical data were presented as numbers and were compared using the chi-square test, continuity correction, or Fisher's exact test as appropriate. A Pearson coefficient was used to determine the correlation between BP and LV mechanical index. $P < .05$ was considered statistically significant. Statistical analyses were performed using the SPSS software 26 (IBM).

3 | RESULTS

3.1 | Basic parameters

Seventy-two patients were divided into DP and non-DP groups according to 24-h ABP patterns at SL. Demographic parameters of the two groups, including age, sex, BMI, race, and smoking and alcohol history are shown in Table 1.

3.2 | Effect of acute HA exposure on BP

Figure 1 depicts the 24-h ABP changes at SL and HA. While 24-h SBP, day-time SBP, night-time SBP, 24-h DBP, day-time DBP, and night-time DBP increased remarkably after acute exposure to HA

in all patients (Figure 1A,B and Table S1). In addition, morning SBP, morning DBP, pre-waking SBP, pre-waking DBP, lowest night-time SBP, and lowest night-time DBP were significantly elevated (Table S1). In particular, HA exposure resulted in markedly increased day-time SBP and DBP (Table S1).

Interestingly, although 24-h SBP and DBP increased in both groups, patients in the DP group showed pronounced incremental increases in night-time SBP and DBP (Table 2 and Figure 1E,F) after HA exposure. In particular, the non-DP group exhibited significant elevation in day-time SBP and DBP (Table 2 and Figure 1C,D), which blunted the difference in nocturnal SBP and DBP fall (Table 2 and Figure S1) and lowest night-time SBP and DBP, as well as evening SBP and DBP between the two groups after acute HA exposure (Table 2). Comparison of variation values also revealed this phenomenon (day-time SBP 9.87 ± 10.43 vs. 4.57 ± 7.99, P = .018; night-time SBP 1.55 ± 11.68 vs. 9.64 ± 7.81, P = .004; night-time DBP 2.53 ± 8.43 vs. 8.40 ± 7.24, P = .002; nocturnal SBP fall 6.34 ± 10.64 vs. −4.67 ± 7.78, P < .001; nocturnal DBP fall 4.94 ± 11.54 vs. −5.80 ± 11.48, P < .001) (Table 2 and Figure S2). In addition, the morning SBP and DBP surge increased in the non-DP group, but reduced in the DP group after acute exposure to HA (morning SBP surge 2.84 ± 20.75 vs. −7.77 ± 23.29, P = .045; morning DBP surge 1.07 ± 14.02 vs. −6.64 ± 16.31, P = .036) (Table 2). Moreover, acute HA exposure increased night-time BP variability in the DP group, but reduced it in the non-DP group (Table 2). The difference in BP variability in two groups was blunted after acute HA exposure, especially in day-time and night-time SBP and night-time DBP (Table 2).

3.3 | Effect of acute HA exposure on LV function

Function indexes of the LV in the total study population at SL and HA are shown in Table S2. EDV and ESV were both significantly decreased. E/e' and E/A were reduced while EF was elevated after exposure to HA. Moreover, ultrasound speckle tracking measurements indicated that the torsion and untwisting rates increased. Furthermore, while there was no significant change in VAC after exposure to HA, Ees and Ea were both obviously elevated. Patients in the non-DP group had lower GLS and higher torsion, whereas other parameters of LV function were similar between the two groups at SL. Patients in the DP group showed significant incremental increases in GLS, torsion rate, and untwisting rate (GLS −0.21 ± 2.21 vs. 1.70 ± 1.40, P < .001; torsion 0.86 ± 4.97 vs. 4.66 ± 3.27, P < .001; untwisting rate 13.58 ± 23.51 vs. 27.85 ± 31.65, P = .033) after acute HA exposure (Table 3). The difference in EF between DP and non-DP groups was pronounced after exposure, which was attributed to a significant decrease in ESV (ESV −2.08 ± 12.74 vs. −8.21 ± 11.70, P = .037) (Table 3). Meanwhile, patients in the DP group showed higher Ees and lower Ea after acute exposure to HA, which resulted in a decrease in VAC. On the contrary, VAC was elevated in the non-DP group (0.04 ± 0.19 vs. −0.10 ± 0.04 P = .001) (Table 3).

3.4 | Correlation of BP and LV mechanics

Results of the evaluation of the effect of cardiac function response on BP during acute HA exposure, which represent left ventricular

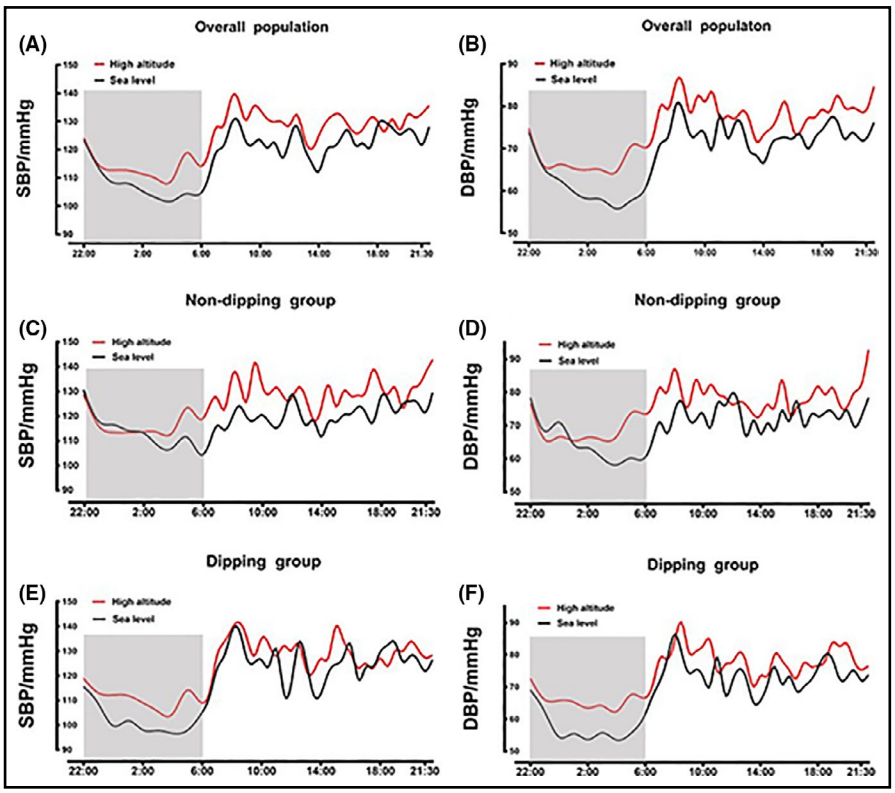

FIGURE 1 Averaged 24-h SBP and DBP profiles in all patients, DP patients, and non-DP patients. (A and B) Averaged 24-h SBP and DBP in 72 patients at SL and HA. (C and D) Averaged 24-h SBP and DBP in the non-DP group at SL and HA. (E and F) Averaged 24-h SBP and DBP in the DP group at SL and HA. DBP, diastolic blood pressure; DP, dipping pattern; HA, high altitude; SBP, systolic blood pressure; SL, sea level

TABLE 2 Effect of acute HA exposure on BP in the DP and non-DP groups

	SL			HA			Variation		
Variables	**Non-DP (*n* = 36)**	**DP (*n* = 36)**	***p* Value**	**Non-DP (*n* = 36)**	**DP (*n* = 36)**	***p* Value**	**Non-DP (*n* = 36)**	**DP (*n* = 36)**	***p* Value**
SpO_2, %	97.17 ± 1.44	97.06 ± 1.64	.917	87.22 ± 2.56	87.19 ± 3.93	.972	−9.94 ± 3.17	−9.86 ± 4.14	.924
24-h HR, bpm	73.12 ± 8.02	73.88 ± 6.81	.667	85.09 ± 8.79	83.57 ± 6.36	.402	11.97 ± 8.46	9.69 ± 7.39	.227
Day-time HR, bpm	75.61 ± 8.16	78.83 ± 7.49	.086	88.56 ± 8.41	87.65 ± 6.68	.613	12.95 ± 8.12	8.82 ± 7.66	.030
Night-time HR, bpm	63.56 ± 10.01	56.32 ± 6.82	.003	72.95 ± 12.01	68.92 ± 9.06	.113	9.39 ± 11.47	12.60 ± 8.99	.190
BP, mmHg									
24-h SBP	118.82 ± 10.76	119.24 ± 6.08	.842	126.79 ± 10.23	124.96 ± 7.89	.400	7.96 ± 9.15	5.73 ± 6.35	.232
Day-time SBP	119.68 ± 11.40	124.30 ± 6.90	.126	129.54 ± 10.33	128.87 ± 9.01	.767	9.87 ± 10.43	4.57 ± 7.99	.018
Night-time SBP	115.42 ± 9.14	101.28 ± 6.31	<.001	116.97 ± 13.63	110.93 ± 8.36	.027	1.55 ± 11.68	9.64 ± 7.81	.004
24-h DBP	70.65 ± 8.00	69.60 ± 4.01	.483	76.46 ± 5.78	75.28 ± 5.39	.372	5.81 ± 5.74	5.68 ± 5.51	.702
Day-time DBP	71.89 ± 8.10	73.06 ± 4.78	.459	78.79 ± 5.47	77.95 ± 5.81	.531	6.89 ± 6.28	4.89 ± 6.66	.188
Night-time DBP	65.84 ± 8.60	57.20 ± 4.00	<.001	68.38 ± 9.76	65.61 ± 7.76	.187	2.53 ± 8.43	8.40 ± 7.24	.002
BP characteristic, mmHg									
Dipping ratio	0.97 ± 0.04	0.82 ± 0.05	<.001	0.90 ± 0.08	0.86 ± 0.07	.024	−0.06 ± 0.11	0.05 ± 0.08	<.001
Nocturnal SBP fall, %	3.31 ± 4.44	18.38 ± 5.27	<.001	9.65 ± 8.29	13.70 ± 6.62	.025	6.34 ± 10.64	−4.67 ± 7.78	<.001
Nocturnal DBP fall, %	8.34 ± 6.88	21.46 ± 6.54	<.001	13.28 ± 10.11	15.65 ± 9.53	.309	4.94 ± 11.54	−5.80 ± 11.48	<.001
Pre-waking SBP	109.57 ± 13.06	97.26 ± 7.40	<.001	118.67 ± 17.19	109.75 ± 13.09	.016	9.10 ± 20.29	12.48 ± 13.19	.404
Pre-waking DBP	59.47 ± 10.45	54.47 ± 4.99	.012	70.36 ± 12.69	65.12 ± 9.90	.084	10.89 ± 14.26	10.65 ± 11.59	.938
Morning SBP	111.63 ± 13.64	116.40 ± 14.02	.148	123.10 ± 13.11	120.66 ± 13.80	.444	11.47 ± 15.65	4.26 ± 18.73	.080
Morning DBP	66.40 ± 10.16	69.76 ± 8.62	.135	77.79 ± 9.51	73.37 ± 10.85	.070	11.39 ± 11.11	3.62 ± 13.18	.009
Morning SBP surge	1.60 ± 13.78	18.88 ± 14.41	<.001	4.44 ± 16.78	11.11 ± 17.92	.029	2.84 ± 20.75	−7.77 ± 23.29	.045
Morning DBP surge	6.36 ± 11.14	15.14 ± 10.63	<.001	7.43 ± 13.84	8.50 ± 11.87	.726	1.07 ± 14.02	−6.64 ± 16.31	.036
Evening SBP	124.49 ± 11.85	113.04 ± 11.34	<.001	122.27 ± 17.62	116.06 ± 14.10	.217	−2.22 ± 19.38	3.01 ± 15.34	.209
Evening DBP	74.08 ± 12.26	65.87 ± 7.51	.001	70.62 ± 10.08	68.72 ± 8.53	.393	−3.46 ± 12.56	2.86 ± 10.43	.023
Lowest night-time SBP	107.93 ± 12.04	95.81 ± 8.50	<.001	113.58 ± 12.53	115.50 ± 13.93	.541	5.65 ± 13.22	19.69 ± 16.26	<.001
Lowest night-time DBP	60.85 ± 11.41	53.71 ± 4.67	.001	63.17 ± 10.10	61.11 ± 8.99	.365	2.32 ± 12.60	7.40 ± 10.47	.067
BP variability, mmHg									
24-h ARVs	16.48 ± 5.47	17.74 ± 3.55	.184	19.00 ± 4.18	19.74 ± 5.78	.532	2.52 ± 5.25	2.00 ± 5.89	.698

(Continues)

TABLE 2 (Continued)

Variables	SL			HA			Variation		
	Non-DP (n = 36)	DP (n = 36)	p Value	Non-DP (n = 36)	DP (n = 36)	p Value	Non-DP (n = 36)	DP (n = 36)	p Value
Day-time ARVs	16.62 ± 5.97	19.56 ± 4.47	.021	20.92 ± 5.28	21.55 ± 6.48	.650	4.30 ± 5.41	2.00 ± 7.21	.130
Night-time ARVs	15.93 ± 7.30	11.84 ± 5.65	.015	13.12 ± 4.75	13.59 ± 7.60	.698	−2.81 ± 10.01	1.74 ± 8.96	.045
24-h ARVd	13.41 ± 5.65	13.01 ± 2.86	.704	15.39 ± 4.44	14.11 ± 4.54	.233	1.97 ± 6.88	1.11 ± 5.14	.188
Day-time ARVd	13.82 ± 5.96	14.27 ± 3.56	.700	16.85 ± 5.79	15.25 ± 5.37	.230	3.02 ± 7.96	0.98 ± 6.32	.232
Night-time ARVd	12.01 ± 8.01	8.59 ± 4.10	.044	10.79 ± 4.77	10.70 ± 5.06	.928	−1.22 ± 9.59	2.11 ± 6.29	.158

Note: Values are presented as mean ± standard deviation.

Abbreviations: ARVd, average real variability of DBP; ARVs, average real variability of SBP; DBP, diastolic blood pressure; DP, dipping pattern; HA, high altitude; HR, heart rate; SBP, systolic blood pressure; SL, sea level.

systolic and diastolic function, are shown in Table 3. Regression analysis revealed that variations in night-time SBP were correlated with torsion variations in the total study population (Figure 2A, R = .751, P < .001), patients in the DP group (Figure 2C, R = .577, P < .001), and patients in the non-DP group (Figure 2B, R = .761, P < .001). Moreover, variations in night-time SBP correlated with variations in GLS (Figure 2D, R = .543, P < .001). This correlation was more significant in the DP group than the non-DP group (Figure 2E,F, R = .593, P < .001). However, there was no obvious correlation between variations in night-time DBP and variations in untwisting rate (Figure 2G–I).

4 | DISCUSSION

To our knowledge, this is the first study to analyze changes in BP characteristics and LV functions following acute exposure to HA in patients with different BP patterns. We found that patients in the non-DP group exhibited remarkable elevations in day-time SBP and DBP rather than night-time SBP and DBP, which represented a different BP pattern change after acute exposure to HA compared with patients in the DP group. Moreover, some parameters that reflect LV systolic mechanics and function, such as GLS, torsion, and EF, underwent significant incremental changes after acute HA exposure. However, these changes did not occur in patients in the non-DP group. Furthermore, we also revealed the correlation between variations in BP and variations in LV systolic mechanics. Variations in GLS and torsion were correlated with variations in night-time SBP in both groups.

4.1 | Clinical significance of non-dipping BP pattern

BP follows a circadian rhythm with 15% lower values at night than during the day. Non-DP showed a blunted decrease in the night-time BP (absence of a nocturnal BP dip) and was considered an impaired circadian BP rhythm. Non-DP has been confirmed to be associated with hypertension, chronic renal disease, and diabetes mellitus. In addition, previous studies indicated that non-dippers showed a more positive link with organ injury compared to patients with normal nocturnal BP fall, including renal dysfunction, brain cognitive dysfunction, and cardiovascular damage.[14] In hypertensive patients with Non-DP, LV GLS, and GCS were significantly lower, indicating the LV mechanics were more impaired in the non-dippers.[15] Although, in our study, the dippers and non-dippers we recruited were healthy volunteers, patients with DP showed a better systolic mechanics and cardiac adaptation during acute HA exposure.

4.2 | Effect and mechanism of acute high-altitude exposure on BP

In HA exposure, BP remains largely unchanged over the first minutes or hours. However, over the next few days, BP increases remarkably,

TABLE 3 Effect of acute HA exposure on LV function in the DP and non-DP groups

	SL			HA			Variation		
Variables	Non-DP (*n* = 36)	DP (*n* = 36)	*p* Value	Non-DP (*n* = 36)	DP (*n* = 36)	*p* Value	Non-DP (*n* = 36)	DP (*n* = 36)	*p* Value
EDV, ml	110.73 ± 20.04	111.92 ± 23.41	.539	102.51 ± 16.93	102.45 ± 20.78	.989	−8.22 ± 21.50	−9.47 ± 22.50	.612
ESV, ml	46.06 ± 9.36	44.99 ± 11.53	.667	43.98 ± 11.03	36.79 ± 8.85	.003	−2.08 ± 12.74	−8.21 ± 11.70	.037
EF, %	58.46 ± 4.11	60.20 ± 4.22	.107	57.51 ± 5.93	64.15 ± 3.86	<.001	−0.95 ± 6.13	3.95 ± 5.54	.001
E/A	1.88 ± 0.62	1.86 ± 0.56	.719	1.41 ± 0.34	1.44 ± 0.38	.734	−0.47 ± 0.57	−0.41 ± 0.59	.778
E/e′	6.74 ± 0.94	6.41 ± 1.17	.184	5.77 ± 1.15	5.91 ± 1.29	.628	−0.97 ± 0.89	−0.50 ± 1.38	.088
GLS, %	19.66 ± 2.30	20.74 ± 1.54	.022	19.44 ± 2.00	22.44 ± 2.19	<.001	−0.21 ± 2.21	1.70 ± 1.40	<.001
GCS, %	25.84 ± 2.65	25.45 ± 2.77	.544	24.85 ± 1.79	25.49 ± 2.92	.265	−0.99 ± 2.56	−0.04 ± 3.37	.148
Torsion, °	12.44 ± 4.02	10.68 ± 2.40	.028	13.31 ± 5.03	15.36 ± 3.87	.057	0.86 ± 4.97	4.66 ± 3.27	<.001
Untwisting rate, °/s	74.05 ± 32.58	80.76 ± 37.61	.421	87.63 ± 28.39	108.60 ± 45.95	.063	13.58 ± 23.51	27.85 ± 31.65	.033
Ees, mmHg/ml	2.41 ± 0.62	2.56 ± 1.29	.783	2.68 ± 0.88	3.13 ± 0.82	.027	0.27 ± 1.01	0.57 ± 1.46	.063
Ea, mmHg/ml	1.69 ± 0.32	1.61 ± 0.38	.347	1.92 ± 0.37	1.73 ± 0.38	.055	0.23 ± 0.48	0.11 ± 0.50	.336
VAC	0.72 ± 0.12	0.67 ± 0.11	.070	0.76 ± 0.19	0.57 ± 0.09	<.001	0.04 ± 0.19	−0.10 ± 0.14	.001

Note: Values are presented as mean ± standard deviation.

Abbreviations: DP, dipping pattern; E/A, peak early diastolic velocity/late diastolic velocity; E/e', peak early diastolic velocity/early diastolic velocity; Ea, effective arterial elastance; EDV, end-diastolic volume; Ees, end-systolic elastance; EF, ejection fraction; ESV, end-systolic volume; GCS, global circumferential strain; GLS, global longitudinal strain; HA, high altitude; SL, sea level; VAC, ventricular-arterial coupling.

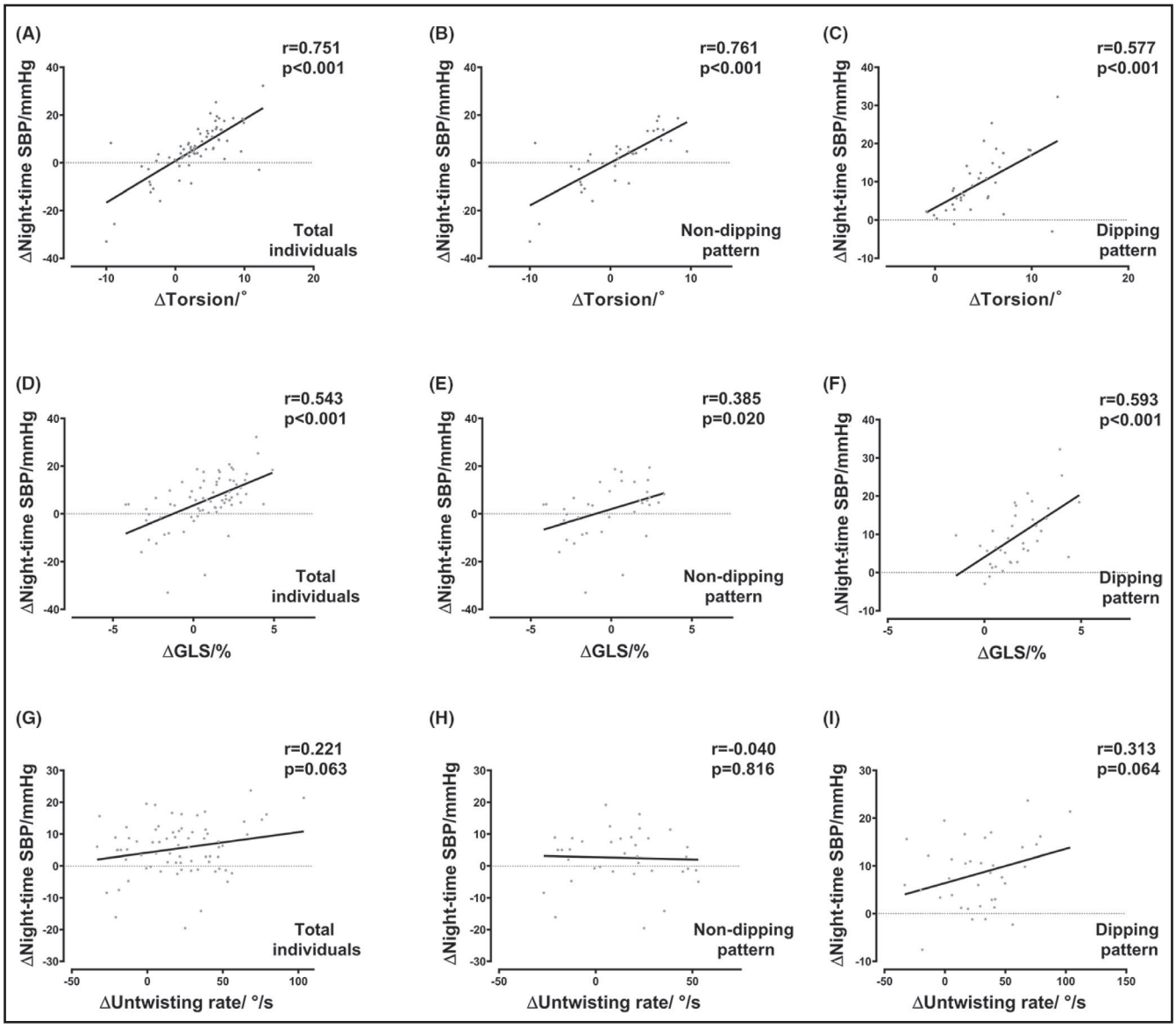

FIGURE 2 Correlation between night-time BP and LV mechanics. (A–C) Correlation between night-time SBP variation and torsion variation in all patients, DP patients, and non-DP patients. (D–F) Correlation between night-time SBP variation and GLS variation in all patients, DP patients, and non-DP patients. (G–I) Correlation between night-time DBP variation and untwisting rate variation in all patients, DP patients, and non-DP patients. BP, blood pressure; DBP, diastolic blood pressure; GLS, global longitudinal strain; LV, left ventricle; SBP, systolic blood pressure. Δ, variation after acute HA exposure

especially in DBP, persists during prolonged altitude exposure, and the rise seems to be continuous and proportional to the altitude reached. It is particularly pronounced in the night-time readings, resulting in a reduction in the nocturnal BP fall, and the circadian rhythm of 24-h BP fluctuations disappears. When returning to SL, BP mostly fall back to baseline.[16] At the beginning, the mechanism was a direct vasodilatory effect of hypoxia counteracting sympathetic activation, including some local regulatory factors, such as production of nitric oxide, ATP release from red blood cells, and changes mediated by hypoxia inducible factor-1.[17] Subsequently, pressor mechanisms begin to dominate. The current belief is that the enhanced sympathetic nerve activity caused by acute altitude hypoxia is related to the sympathetic reflex caused by chemoreceptors in the carotid sinus and aortic arch, and this stimulates the release of catecholamines.[18] Parati and colleagues[2] have also confirmed this point that while the activity of the renin-angiotensin-aldosterone system was inhibited, the secretion of vasoconstrictor factors also increased, resulting in peripheral vascular resistance increases caused by contraction of the smooth muscle arterioles.[19] Since hypoxia has a greater impact on arterial elasticity, the change in DBP is more obvious.[17] Factors such as endothelin-1 levels and erythropoietin are also likely to be involved.[20]

4.3 | Mechanism of night-time BP variation after acute HA exposure

Previous study has found the increase in BP is more pronounced at night than during the day with acute exposure to HA.[2] Several potential mechanisms might account for this phenomenon. Nocturnal BP

values are always lower compared with day-time values, which might be more likely to cause a chemoreflex-induced increase in sympathetic activity. On the other hand, poor sleep quality and occurrence of central apnea at HA may contribute to nocturnal blood oxygenation reduction.[21] Furthermore, impaired renal capacity to excrete sodium has been shown to be a factor resulting in a blunted nocturnal BP fall. The nocturnal BP increase via the pressure-natriuresis mechanism is a likely compensatory mechanism to preserve sodium balance.[22] Interestingly, we found that this phenomenon of night-time BP change was typical in DP groups, but not significant in the non-DP group. Little information on BP pattern changes during HA exposure in non-DP patients has been reported to date. In our study, differences in oxygen saturation between the two groups did not achieve statistical significance, which seemingly indicated that the absence of a compensatory response in non-DP patients may be due to reduced sensitivity to hypoxia.

4.4 | Effect and mechanism of acute HA exposure on LV function and mechanics

LV function and mechanics experienced changes at acute HA. ESV and EDV were markedly reduced, but cardiac output remained substantially unchanged because of a reduction in stroke volume.[23] Although the E/A ratio was significantly decreased compared to the baseline levels with acute exposure to HA,[24] diastolic relaxation was not acutely impaired as untwisting velocity increased. LV systolic function was elevated with increased LV twist mechanics, and a compensatory increase countered the suggestion of a direct impairment of systolic function at HA.[25] These variations demonstrated that LV mechanics had a key role in preservation of cardiac function during HA trekking. Meanwhile, previous studies have also revealed that LV systolic strain rates were enhanced at HA. EF was slightly higher after acute HA exposure, but still not enough to achieve statistical significance.[26] Potential mechanisms might be explained as follows: Changes in myocardial contractile force stimulated by hypoxia and increased local catecholamine hormone levels. Diastolic function may change before systolic function. Elevated pulmonary artery pressure causes an increase afterload in right ventricular, affecting LV filling and leading to compensatory contractility changes. The decrease in body fluid volume may have an impact on the left cardiac preload, leading to changes in LV mechanics.[27]

In our investigation, we found that there was a significant elevation of EF in DP patients compared with non-DP patients. Moreover, E/e' seemingly decreased in non-DP patients, indicating that cardiac systolic and diastolic function impairments were more significant after acute HA exposure in non-DP subjects. Furthermore, LV twist mechanics parameters measured by two-dimensional ultrasound speckle tracking failed to show an obvious increase of torsion and GLS, which revealed that non-DP patients lost the compensatory response of the LV twist mechanics. Furthermore, the increment of untwisting in DP patients was lower compared with non-DP patients. Previous study had found the changes in LV cardiac mechanics may be related to the BP changes. Peripheral hyperemia did cause a significant increase in LV twist, and blood flow restriction reduced LV twist and untwisting rate conversely.[28] The heart always serves as an important target organ, as undergoing traumatic changes under the influence of elevated BP over a long period of time, including mechanical and functional damage changes in the LV.[29] However, this short-term mechanical adaptation to elevated BP in acute HA conditions is more likely to be interpreted as a compensatory change that maintains normal physiological function.

4.5 | Correlation of BP and LV mechanics and potential meaning significance

Furthermore, we first used VAC, which plays a major role in the physiology of cardiac and aortic mechanics in this study, to further evaluate functional variations in LV after HA exposure. Ees represented the necessary intracavitary pressure to increase the volume, while Ea indicated the degree of arterial elastic resistance.[12] We found a significant difference in VAC variations between the two groups, which revealed that the effect of myocardial contractility elevation was greater than increased arterial elastic resistance in DP patients than in non-DP patients, consistent with the LV mechanics variations found above. Interestingly, we also found that LV torsion and GLS were correlated with the compensatory increase in nighttime SBP. BP changes more obvious during nighttime compared with daytime, and LV mechanics underwent adaptive changes in dipping patients when acute HA. While the changes did not appear in non-DP group. In line with our results, the high BP of non-DP patients might come from the over-activation of vasoconstriction, but did not accompanying an elevated LV function and mechanics. Therefore, we supposed that non-DP might be a harmful factor in acute HA exposure. Previous studies found that LV twist and untwisting rate were significantly impaired in the hypertensive patients, always indicating damage of LV myocardial function.[30] Whether, there is more obvious structural damage in non-DP patients compared with DP group remains to be confirmed. Furthermore, the exact molecular mechanisms involved in various BP changes in the two groups remain unknown.

4.6 | Limitations

This study had several limitations due to the limited research condition at HA. Firstly, the study patients were mostly young Chinese people from the Han population. With a narrow study population, the application of our present findings may be limited. Secondly, we did not examine changes in biochemical indexes in this study, potential molecular mechanism remains to be further studied to explain this phenomenon. Moreover, due to the difficulty of carrying a large population field study on the plateau, we did not perform diary card to record the time of sleep and awakening during the monitoring. Besides, although all the patients we enrolled had baseline 24 h-BP at sea level < 130/80 mm Hg, there still has the possibility of some masked hypertensive patients.

5 | CONCLUSIONS

Little information is known about heart and BP responses of different ambulatory BP patterns after acute HA exposure. Our study demonstrates that acute HA exposure increases BP in dippers at night, while non-dippers showed day-time increases. Furthermore, enhanced left ventricular torsion and global longitudinal strain are associated with BP changes. Non-dippers showed poor cardiac compensatory and maladaptive to acute HA exposure. To our knowledge, this is the first study to analyze changes in BP characteristics and LV functions following acute exposure to HA in patients with different BP patterns. However, the exact mechanisms involved need to be further illuminated.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

RC, JY, CL and LH worked on the conception of the study. RC, YY, YS, JK, FY, CH, RC, HL, ZC and WG contributed to the data collection. CL, and JY checked the data. RC, YS, and RC performed the statistical analysis. RC, and JY drafted the manuscript. XG, HT, JZ and LH reviewed the manuscript. All authors read and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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