

Systemic Blood Pressure, Arterial Stiffness and Pulse Waveform Analysis at Altitude

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Abstract

Objectives: Systemic arterial pressure rises on acute exposure to high altitude and changes in blood pressure (BP) and endothelial function may be important in the pathogenesis of clinical syndromes occurring at high altitude.

Methods: Arterial BP, stiffness (SI) and tone (RI) were studied over 11 days in 17 subjects (three having mild hypertension) ascending to 3,450m and 4,770m using a non-invasive, finger photoplethysmography technique.

Results: At 3,450m BP rose from mean 131/75 mmHg (SD 23/12) to 145/86 (23/12) and was maintained at this level ($p < 0.001$). SI did not change significantly from 8.5 m/sec (2.5) to 9.7 (3.2). RI fell during the first day at 3,450m from 74.4% (7.9) to 70.5% (13.8) (NS $p > 0.05$) and to 69.9% (12.0) ($p < 0.02$) at 4,770m but then reverted to baseline. Changes in SI and RI did not relate to changes in blood pressure. Changes in both arterial stiffness and tone were similar in those who developed AMS compared with those who did not. Baseline SI tended to be higher in the three subjects with hypertension 11.1m/sec (SD 2.7) compared with the normotensives 8.3 m/sec (SD 2.7) (NS) and baseline RI lower 74.7% (7.0) compared with the normotensives 76.5% (8.5) (NS). Changes in SI and RI at altitude in the hypertensive subjects were similar to the non-hypertensive subjects.

Conclusions: We conclude that acute exposure temporarily affected endothelial function as measured by a change in vascular tone but this did not predict the development of AMS. The rise in arterial BP was not related to changes in arterial stiffness or tone.

Introduction

Modest increases in systemic arterial pressure occur on acute exposure to high altitude, the rise persisting for 10-21 days and then usually reverting to baseline [1,2]. On prolonged residence at high altitude systemic blood pressure tends to be lowered. The principal effect of acute hypoxia appears to be increased sympathetic activity, with little or temporary rise in epinephrine concentrations and a delayed and sustained rise in norepinephrine concentrations coinciding with a rise in arterial pressure [3,4]. The acute effects of hypoxia can be reversed by oxygen, propranolol or prazosin. Changes in systemic blood pressure appear to be greater in known [5] or borderline hypertensives [6] with greater rises noted on acute exposure to altitude. Basal pulse wave velocity did not differ in sea level natives acutely exposed to 5,050m compared with high altitude natives, but greater increases in blood flow velocity occurred in response to muscular ischaemia in the high altitude natives [7]. No previous studies of vascular stiffness and tone have been reported at altitude.

Changes in blood pressure and endothelial function may be important factors in the pathogenesis of clinical syndromes occurring at high altitude, including acute mountain sickness

(AMS), high altitude cerebral oedema (HACE) and high altitude pulmonary oedema (HAPE). Although no difference was noted in the systemic blood pressure response in those who developed AMS compared with those without AMS at 4,559m, AMS correlated with a higher proportion of blood pressure variability in those who developed AMS suggesting that an exaggerated chemoreflexic vasoconstriction may be important in the pathogenesis of AMS [8]. We have undertaken studies of arterial stiffness and tone to investigate the mechanism of blood pressure rises on acute exposure to altitude and to assess any relationship these changes may have to the development of AMS. Our hypotheses were that changes in vascular resistance might predict the hypertensive response on exposure to moderate altitude, that changes in vascular tone might be related to the development of AMS and that a short period of acclimatisation might reverse these changes. Serial measurements of arterial stiffness and tone were made during a trek to high altitude in Ladakh.

Methods

Seventeen subjects (13 male), mean age 42 (SD 14.7) years (range 23-68), mean BMI 24.3 (SD 2.8) kg/m² (range 18.8-31.2) were studied. All were non-smokers and none were taking prophylactic drugs for AMS. Three subjects had controlled hypertension but only one was on medication (irbesartan, amiloride, doxazosin and atenolol). The treated hypertensive subject also had type 2 diabetes treated with gliclazide. The

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Day	n	Altitude m	Heart rate beats/min	Systolic BP mmHg	Diastolic BP mmHg	Mean BP mmHg
Baseline	17	80	60 (9.0)	131 (23)	75 (12)	94 (15.4)
Day 1	17	3,450	66 (10.4)*	134 (18)	77 (13)	95 (13.4)
Day 2	17	3,450	59 (11.8)	145 (23) [§]	86 (12) [§]	106 (13.9)
Day 3	16	3,450	63 (8.5)	147 (22) [§]	88 (12) [§]	107 (12.8)
Day 4	17	3,450	60 (8.6)	142 (22) [§]	86 (10) [§]	105 (13.4)
Day 8	15	4,770	66 (10.7)*	146 (20) [§]	85 (9) [§]	105 (12.0)
Day 11	15	3,450	52 (11.1)*	143 (27) [§]	86 (10) [§]	105 (14.1)

Results are given as mean (SD). * $p < 0.05$, $^{\S}p < 0.001$ compared with baseline

Table 1: Altitude profile, heart rate and blood pressure changes

remaining 14 subjects were healthy. All subjects gave informed consent and the study was approved by the South Birmingham Research Ethics Committee

The route profile is given in Table 1. AMS scores were derived from twice daily self-completed Lake Louise Questionnaires. Subjects were considered to have AMS if the score on a single questionnaire was three or more, including headache. Systemic blood pressure (BP) and pulse contour analysis (PCA) were recorded in all subjects in the morning or in the evening. On the third day at altitude measurements were made in both morning and evening in 14 of the 17 subjects. Subjects avoided stimulants such as tea and coffee for at least two hours and rested supine for two minutes before the recordings were made. Blood pressure was measured from the brachial artery using a digital blood pressure monitor UA 767 (A & D Medical, Abingdon, Oxford) at the same time as the first and third pulse waveforms were being recorded in the opposite arm. Pulse waveforms were recorded using a Pulse Trace PT1000 (Micro Medical Ltd, Rochester, Kent; now Carefusion, Chatham, Kent) from a finger photoplethysmographic device applied to a warm index finger. Three readings were taken one minute apart on each occasion. Measurements from one subject were not obtainable on Day 3. There was no significant diurnal variation in heart rate, blood pressure, stiffness index or reflection index and the mean of the morning and evening results have been used for Day 3.

Data Analysis.

The mean of the three pulse contour measurements was used for analysis. Large artery stiffness (stiffness index, SI) in m/sec was derived from the time between the systolic and the reflected pulse wave peaks divided by the height of the subject in metres. Vascular tone (reflection index, RI) as a percentage was derived from the height of the reflected peak divided by the height of the systolic peak x 100.

Statistical analysis

Results are shown as mean (SD) and were considered significantly different when $p < 0.05$. The initial acute response to altitude was analysed by repeated measures (day) ANOVA with differences located using Tukey's HSD test and KaleidaGraph Version 4 Synergy Software (Reading, PA, USA). The response to the higher altitude was assessed by comparing Day 4 and Day 8 results and the effect of partial acclimatisation by comparing baseline to Day 11 (paired t tests). The relationship between variables is expressed using Pearson product-moment correlation coefficient (r).

Results

Pulse rate

Pulse rate (Table 1) rose temporarily on Day 1 on acute exposure to 3,450m ($p < 0.02$) and again at 4,770m ($p < 0.001$). Pulse rate was lower than baseline on Day 11 ($p < 0.05$). Mean pulse rate of subjects with AMS was not significantly different from those without AMS.

Blood pressure

Baseline systolic blood pressure (Table 1) correlated with age (Pearson correlation co-efficient $r = 0.7$ $p < 0.001$). Systolic blood pressure rose on Day 2 ($p < 0.001$) and remained elevated thereafter. Baseline systolic blood pressure was significantly lower in those seven subjects who subsequently developed AMS, 120 (SD13) mmHg compared with the ten subjects who did not 139 (SD 25) mmHg ($p < 0.01$) but the changes with altitude were similar in the two groups. Baseline diastolic blood pressure was correlated with age ($r = 0.55$, $p < 0.001$). Diastolic blood pressure rose on Day 2 ($p < 0.001$) and remained elevated thereafter. Baseline diastolic blood pressure was significantly lower in the seven subjects who subsequently developed AMS 68 (SD 9) mmHg compared with the ten subjects who did not 80 (SD 12) mmHg ($p < 0.001$) but the changes with altitude were similar in the two groups (Table 2). Pulse pressure was unchanged during the study compared with baseline.

Stiffness Index

Baseline SI (Figure 1) was correlated with age ($r = 0.62$ $p < 0.01$) and with baseline mean blood pressure ($r = 0.76$ $p < 0.001$). There was a small increase in mean SI on Day 4 ($p < 0.05$) but otherwise SI remained stable throughout the study and SI on Day 11 of 8.3m/sec (SD 3.2) was not significantly different from baseline. Baseline SI was lower in the seven subjects who subsequently developed AMS 7.1m/sec (SD 1.7) compared with the ten subjects who did not 9.6 m/sec (SD 2.6) ($p < 0.001$) but changes with altitude were similar in the two groups (Table 2).

Reflection Index

Baseline RI was not correlated with age or baseline mean blood pressure. Mean RI tended to fall on acute exposure to both altitudes, the change being insignificant between baseline and day 2 but significant from 79% (SD 9.5) on Day 4 to 70% (SD 12.3) on Day 8 ($p < 0.02$). RI on Day 11 (80% (SD 11.7) was not significantly different from baseline. Changes in RI did not relate to changes in mean blood pressure. There were no significant

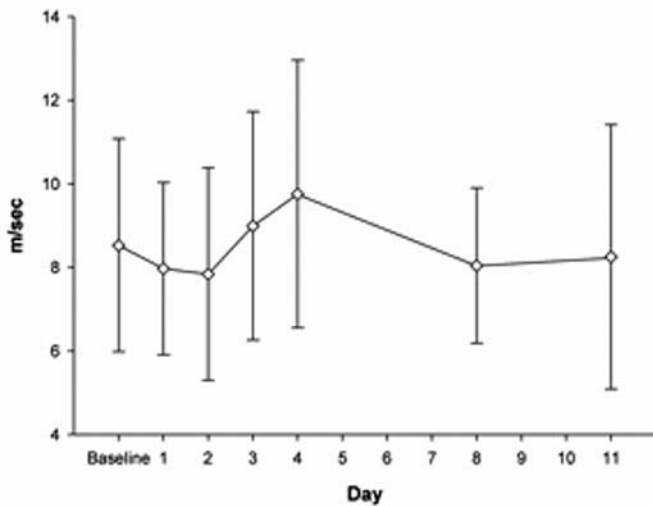


Figure 1. Stiffness index; 0=baseline, days 1-11 at high altitude. Stiffness index on day 4 was higher than baseline ($p<0.05$)

differences in baseline or response of RI to altitude in those with or without AMS (Table 2).

Hypertensive subjects.

Baseline SI tended to be higher in the three subjects with hypertension 11.1m/sec (SD 2.7) compared with the normotensives 8.3 m/sec (SD 2.7) and baseline RI lower 74.7% (7.0) compared with the normotensives 76.5% (8.5) but these differences were not significant. Changes in SI and RI at altitude of the hypertensive subjects were similar to the non-hypertensive subjects.

Discussion

The main findings of the study were a rise in systemic blood pressure, a temporary fall in vascular tone at the two altitudes without associated change in vascular stiffness. Acute exposure to altitude was associated with a rise in systolic and diastolic blood pressure and, as has been noted in other studies [5], the rise was greater in the known hypertensive subjects. Although baseline

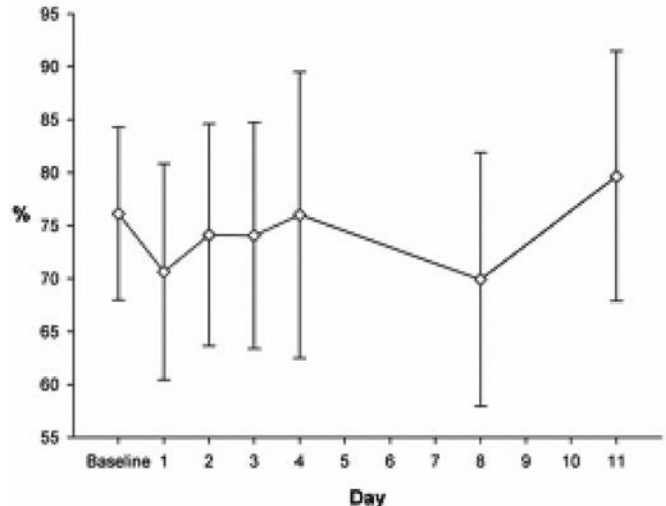


Figure 2. Reflectance index; 0=baseline, days 1-11 at high altitude. Mean reflectance index was reduced on day 8 compared with baseline ($p<0.02$).

mean blood pressure was correlated with stiffness index, the rise in blood pressure was not associated with changes in stiffness index or reflectance index apart from a small, temporary rise in stiffness index which was seen on the fourth day at high altitude. The fall in tone on initial exposure to 3,450m was repeated at 4,770m and would appear to be an acute response to hypoxia on both occasions. Both stiffness and tone on Day 11 had effectively returned to baseline levels but may have been affected by slower pulse rate induced by greater physical fitness or fall in sympathetic activity. The pattern of changes in stiffness and reflectance indices observed at altitude was not different in the hypertensive subjects so they have been included in the main analysis. Similarly, changes in the older subjects were the same as the younger subjects.

Our results failed to show any relationship between changes in arterial stiffness or tone and the development of AMS. However the number of subjects studied was small, the altitude profile resulted in relatively mild symptoms and the subjects spanned a

	Baseline	Day 1	Day 2	Day 3	Day 4
Systolic arterial blood pressure (mmHg)					
AMS	120 (13)*	125 (12)	132 (19)	133(13)	130 (18)
No AMS	139 (2)	140 (20)	154 (23)	154 (24)	150 (23)
Diastolic arterial blood pressure (mmHg)					
AMS	68 (9) [§]	70 (7)	79 (10)	80 (7)	80 (8)
No AMS	80 (12)	82 (15)	90 (11)	92 (12)	90 (9)
Stiffness index m/sec					
AMS	7.1 (1.7) [§]	7.0 (1.8)	6.3 (1.0)	7.4 (1.6)	8.0 (2.9)
No AMS	9.6 (2.6)	8.6 (2.0)	8.7 (2.8)	9.7 (3.0)	11.0 (3.0)
Total	8.5 (2.5)	8.0 (2.0)	7.7 (2.5)	8.9 (2.8)	9.7 (3.2)*
Reflectance index %					
AMS	74.4 (7.9)	70.5 (13.8)	68.6 (13.9)	73.7 (16.5)	71.5 (20.6)
No AMS	75.5 (10.1)	69.3 (6.9)	78.3 (4.8)	75.7 (7.2)	79.5 (7.0)
Total	76.1 (8.1)	70.7 (10.2)	74.1 (10.5)	73.9 (10.7)	76.1 (13.5)

AMS =Acute Mountain Sickness AMS n=7 No AMS n=10 Results are mean (SD)

* $p<0.05$ stiffness index compared with baseline

[§] $p<0.01$ and [§] $p<0.001$ comparing baseline systolic and diastolic blood pressure and stiffness index in those who subsequently did or did not develop AMS.

Table 2: Blood pressure, stiffness and reflectance indices and acute mountain sickness at 3,450m

wide age range. Results may have been affected by a tendency for AMS subjects to be younger than non-AMS subjects and the younger subjects had lower blood pressure, lower arterial stiffness and lower arterial tone. In contrast, a report of borderline hypertensive subjects studied for eight hours in a chamber at a simulated altitude of 4,200m showed more AMS, an antidiuresis and a moderate increase in mean arterial blood pressure unlike the normotensive subjects who had more stable responses [6].

Pulse wave velocity is a measure of arterial stiffness [9]. Finger photoplethysmography is a well-established technique and has been shown to correlate well with simultaneously measured radial pulse wave forms [10] and has been reviewed recently [11]. The equipment has been well validated at sea level and there is no reason to believe would be affected by altitude. Stiffness index is affected by both large and relatively small arteries. The technique is easily applied and measurement of digital volume pulse has a coefficient of variation of 8.8% when measured three times at weekly intervals [12]. Results of pulse contour analysis reflect functional and structural changes in the arterial wall and so may be affected by physiological variables such as age [12], heart rate and blood pressure [13] and by disease states such as arterial hypertension [14], diabetes mellitus [15,16]. Our results showing a relationship of SI to age and blood pressure are consistent with these findings and the absence of any change at altitude might have been predicted. The reflectance index of the digital volume pulse is mainly related to tone in small arteries and changes correlate with flow-mediated dilatation and are impaired in some studies of endothelial dysfunction [17]. Our finding of a temporary change in reflectance index on acute exposure to both altitudes without a change in arterial blood pressure is similar to other reported findings [18]. This suggests there are acute changes in endothelial function with hypoxia but recovery of reflectance index suggests that endothelial function rapidly returns to normal. Further studies at higher altitudes and in older and hypertensive subjects would help to clarify whether changes in tone at altitude are important.

Conclusion

A rise in mean systemic blood pressure on ascent to high altitude was associated with a temporary reduction in vascular tone but no change in vascular stiffness as measured by digital pulse contour analysis. No relationship was found between changes in blood pressure, arterial stiffness or tone and the development of AMS.

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