The effect of High Altitude on Central blood pressure and arterial stiffness

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Central arterial systolic blood pressure (SBP) and arterial stiffness are known to be better predictors of adverse cardiovascular outcomes than brachial SBP. The effect of progressive high altitude (HA) on these parameters has not been examined.

Ninety healthy adults were included. Central BP and the augmentation index (AI) were measured at the level of the brachial artery (Uscom BP+ device) at <200m and at 3619m, 4600m and 5140m. The average age of the subjects (70% men) were 32.2±8.7 years. Compared with central arterial pressures, brachial SBP (+8.1±6.4 mmHg; p<0.0001) and pulse pressure (+10.9±6.6 mmHg; p<0.0001) were significantly higher and brachial DBP was lower (-2.8±1.6 mmHg; P<0.0001). Compared <200m, HA led to a significant increase in brachial and central SBP. Central SBP correlated with AI (r=0.50; 95% CI: 0.41 to 0.58: p<0.0001) and age (r=0.32; 21to 0.41: p<0.001). AI positively correlated with age (r=0.39; p<0.001) and inversely with subject height (r=-0.22; p<0.0001) weight (r=-0.19; p=0.006) and heart rate (r=-0.49: p<0.0001). There was no relationship between acute mountain sickness scores (LLS) and AI or central BP. The independent predictors of central SBP were male sex (coefficient, t 4.7; P<0.0001), age (t=3.6; p=0.004) and AI (t=7.5; p<0.0001; overall r2 =0.40; p<0.0001). Subject height (t=2.4; p=0.02), age (7.4; p<0.0001) and heart rate (t=11.4; P<0.0001) were the only independent predictors of AI (overall r2=0.43; p<0.0001). Central BP and AI significantly increase at HA. This rise was influenced by subject-related factors and heart rate but not independently by altitude, LLS or SpO2.

Introduction

Cardiovascular death is a leading non cause of non-traumatic deaths in adults at high altitude (HA).[1] Despite this fact, there has been limited research into cardiovascular risk assessment at HA. [1] HA exposure leads to an increase in resting heart rate, compared with that at sea level, yet paradoxically, maximal heart rate is reduced.[2] The stroke volume rise noted with exercise at sea level is blunted at HA.[2,4] Consequently, whilst resting cardiac output is higher at HA, versus sea level, at peak exercise it is comparatively lower.[2,4,5] These factors along with the notable reduction in arterial oxygen content act to limit peak exercise capacity and oxygen consumption.[2,5] Other reported cardiovascular responses include an increase in resting brachial artery systolic blood pressure (SBP) and 24hour arterial blood pressure (BP), which along with the increase in resting heart rate could be potential implicating factors in the increased cardiovascular risk.[6-9]

The effects of HA on central arterial haemodynamics, such as central arterial BP and large artery stiffness, are far less well understood and have been barely reported. Central arterial BP and large artery stiffness are known to be more powerful predictors of adverse cardiovascular outcomes, including stroke and cardiovascular death than brachial artery BP as they more closely reflect the haemodynamic loading of vital central organs such as the heart, brain and kidneys.[10.11] Brachial artery BP does not reliably reflect central BP due to the effects of peripheral amplification which is highly variable between individuals.[10,11]

Unfortunately, the accurate non-invasive assessment of central BP and large artery stiffness has been traditionally very difficult. It had required the need for either arterial catheterisation or less portable and expensive non-invasive equipment limiting its research utility at HA, explaining the paucity of published research at genuine terrestrial HA.[5.7]

In the only study to investigate the influence of terrestrial HA on both large arterial stiffness and central BP Parati et al observed a significant increase in both central SBP and the arterial augmentation index (AI, marker of arterial stiffness) in untreated subjects travelling to HA.[7] However, the altitude gain was very rapid (4559m within 28 hours of ascent) and only a single altitude was studied. Nevertheless, their findings are potentially important given the huge numbers exposed to HA worldwide.[1,2]

The Uscom BP$^+$ is a novel device which is able to estimate central blood pressure using a simple oscillometric BP cuff on the upper arm.[12] It has shown excellent agreement with catheter based assessments of central BP and gold standard measures of arterial stiffness.[1315] It utilises pulse wave analysis to assess the AI which reflects the enhancement (augmentation) of central aortic systolic pressure by reflected arterial pulse waves. It has the advantage over several competing devices. It is highly portable and only requires the use of an upper arm cuff therefore avoiding the need to assess either the radial or digital pulse where the signal to noise ratio may be less favourable.

In this study we sought to utilise this available technology to investigate, for the first time the effects of a step-wise increasing terrestrial HA on both central BP and AI during a trek to >5000m.

Methods

Study design and participants

Ninety healthy British Military servicemen aged >18years were included. The subjects were assessed at near sea level (<200m) and during progressive ascent in the Dhaulagiri region in the Himalayas in March/April 2016. Health status was confirmed following a detailed baseline questionnaire. All subjects were assessed to be medically fit for a high altitude venture by their general practitioner. Key exclusion criteria included a history of hypertension and/ or atrial fibrillation. All participants were low altitude dwellers and none had prior exposure to >1400m terrestrial altitude in the four weeks prior to this study. The subjects were studied consecutively in groups of 8-10 individuals with a two day stagger between successive groups. HA related symptoms were assessed using the Lake Louis Scoring System (LLS).[16,17]

High Altitude Ascent and descent profile

The subjects flew from the UK to Kathmandu (1400m day 1-3) where they underwent a short period of local acclimatisation at 1400m. From there they travelled by a staged road move to Darbang (1030m) then on foot with loads of up to 12kg over the ensuing 11 days to HA of 5140m (after passing over French pas at 5360m) (figure 1). Thereafter, they descended on foot and then by road back to Kathmandu. Research assessments were performed at sea level and at static research camps at 3619m, 4600m and 5140m during ascent.

Physiological assessments and central blood pressure measurement

Oxygen saturations (SpO_2) were measured using a Nonin Onyx (Nonin Medical Inc, Plymouth, Minnesota) pulse oximeter. Blood pressure and arterial stiffness assessments were obtained at the same time using an Uscom BP^+ device (Uscom, Sydney, NSW, Australia as previously reported.[13-15] The upper arm cuff was attached to the dominant arm of seated subjects. All subjects were rested for at least five minutes prior to BP assessment and they were not permitted to drink caffeine or smoke for at least three hours and alcohol for ≥10 hours prior to BP measurements.[18] The subjects were advised not to speak during the recordings. The BP^+ device measures both central and peripheral BP (mmHg) using supra systolic oscillometry. Following an initial inflation-deflation the cuff is re-inflated to approximately ≥30mm Hg above the recorded suprasystolic pressure for 10 seconds, during which suprasystolic BP and pulse wave assessments are recorded via the arm cuff. All recordings were stored on a mini SD card within the device and later exported for data analysis. Only readings with a signal-to-noise ratio of ≥6 was were included and tests with a ratio of <6 were repeated.

The BP^+ calculates a number of additional haemodynamic indices that were of interest to this study, including the AI. Its quoted AI is the arterial augmentation pressure (difference between the second and first systolic peaks of the central pressure waveform) expressed as a percentage of the pulse pressure and it is an *indirect* measure of large arterial stiffness. Further parameters that we were specifically interested in for this study were the time to systolic wave Reflection (TR) and the suprasystolic pulse pressure variation (ssPPV). The reflected Wave Transit Time is an indirect measure of pulse wave velocity and large arterial stiffness. The ssPPV is a novel measure of fluid responsiveness and is heavily influenced by respiratory variation and left ventricular stroke volume, both of which can be affected at HA.[19-21] The BP^+ calculates the ssPPV as the difference between maximum and minimum pulse pressures divided by the average pulse pressure over the 10 second rhythm strip.

Ethics

Participation was entirely voluntary and all participants underwent detailed written informed consent. The study was approved by the Ministry of Defence Research and Medical Ethics Committee (MODREC) and was conducted according to the standards of the declaration of Helsinki.

Statistical analysis

Data were analysed using GraphPad InStat version 3.05 and with all graphical figures presented using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA, USA). Sample size calculations were performed using a proprietary determined sample- size calculator using (GraphPad StatMate version 2.00 for Windows). The Kolmogorov-Smirnov test was undertaken to assess normality of all continuous data and all continuous data are presented as mean ± standard deviations. Comparison of unpaired data was performed using an unpaired T test or the Mann-Whitney Test for parametric and non-parametric data respectively and with a paired t test and Wilcoxon matched pairs test for equivalent paired data. Continuous data from ≥3 groups were compared using a one-way Analysis of Variance (ANOVA) with either Tukey post-hoc tests or a Kruskal-Wallis test with Dunn post-test for parametric and non-parametric data respectively. Correlations were performed using Pearson and Spearman rank correlation (±95% confidence interval, CI) for parametric and non-parametric data respectively. A two tailed *P* value <0.05 was considered statistically significant for all comparisons. All univariate predictors of central arterial systolic blood pressure were entered into a multiple linear regression analysis model in order to identify its independent predictors. A two tailed *P* value <0.05 was considered statistically significant for all comparisons.

Sample size calculations

Parati et al studied 44 subjects who travelled form sea level to 4559m within 29 hours.[8] From this group there were 22 subjects who were randomised not to receive prophylactic medication to prevent acute mountain sickness. In this group they observed a non-significant increase in central systolic blood pressure from 103.7±10.7 to 108.8±8.0 mmHg from sea level to that after 48h at HA. The AI significantly increased at HA versus sea level. Based on this data and the average standard deviation of their central BP readings, we calculated that a sample size of at least 60 subjects would have >80% power to detect a $\geq$5 mmHg change in central SBP and a $\geq$7% change in AI at HA at a significance level (alpha) of 0.05 (two-tailed).

Results

Ninety subjects were included. The average age of the subjects were 32.2±8.7 years with 70% being male. Heart rate and LLS increased and SpO_2 fell at HA compared with sea level (table 1).

Overall brachial arterial SBP (+8.1±6.4 mmHg; p<0.0001) and pulse pressure (+10.9±6.6 mmHg; p<0.0001) were significantly greater than that observed centrally. Conversely the brachial artery DBP was lower (-2.8±1.6 mmHg; P<0.0001) than the equivalent central readings.

Compared with baseline sea level values there was a significant increase in both brachial and central SBP and in brachial but not central arterial pulse pressure at HA (table 2). The highest increase in both brachial and central SBP was between sea level and 4619m (+6.1±13.30 and +7.1±5.5 mmHg respectively) (table 2; figure 2).

The AI and ssPPV both increased at HA whereas the reflected wave transit time and systolic ejection period decreased versus sea level (table 2; figure 3). Adjusting the AI to an average heart rate of 75 per minute (AI@75) did not alter the findings.

There were significant correlations between central SBP and both AI (r=0.50; 0.41 to 0.58: p<0.0001) and age (r=0.32; 21to 0.41: p<0.001). Other independent, albeit weak predictors, of central SBP were SpO_2 (r=-0.14 -0.25 to -0.05: p=0.02), heart rate (r=-0.16; -0.27 to -0.05: p=.003) male sex (r =0.15; 046 to 0.26: p=0.004) ethnicity (r=0.15; 0.04 to 0.25: p=0.007) smoking status (r=0.18; -0.28 to -0.07; p=0.001) and altitude (r=0.10; p=0.05). AI positively correlated with age (r=0.39; p<0.001) and inversely with subject height (r-0.22; p<0.0001) weight (r-0.19; p=0.006), and heart rate (-0.49: p<0.0001). There was no relationship between LLS and either AI or central BP.

Multivariate analysis was performed to assess the independent predictors of central systolic BP. Only the univariate predictors were included in the model. The independent predictors of central SBP were male sex (coefficient, t 4.7; P<0.0001), age (t 3.6; p=0.004) and AI (t 7.5; p<0.0001; overall r^2 =0.40; p<0.0001). If AI was removed from the model (overall r^2=0.29; p<0.0001) then the independent predictors of central systolic BP were age, heart rate and smoking history. Subject height (coefficient 2.4; p=0.02), age (7.4; p<0.0001) and heart rate (11.4; P<0.0001) were the only independent predictors of AI (overall r^2=0.43; p<0.0001). The order of the trekking groups did not influence the findings when included in the multivariate analysis.

Discussion

To the author's knowledge, this is the first study to assess the effects of stepwise increasing terrestrial HA on arterial stiffness and central BP over a conventional and progressive HA trek. We found that HA exposure led to a significant increase in central SBP and AI. Neither altitude nor the SpO_2 were independent predictors of AI and central SBP. Heart rate was a significant determinant of both AI and central BP.

HA exposure leads to a wide range of complex effects on both the pulmonary and systolic circulation which have been well described.[2,4,5,22] Hypobaric hypoxia leads to widespread sympathetic activation leading to an increase in resting heart rate .[23-25] The reported effects on BP are variable and are highly dependent on the degree of hypoxia and speed and duration of exposure. Furthermore, the type of hypoxic environment may be a major confounder.[26] Several previously published studies have used simulated hypoxia (using either a normobaric or hypobaric chamber) in an attempt to replicate the degree of hypoxia observed at genuine HA.[4,22,25,26] However, simulated hypoxia does not reproduce the environmental and geographical effects genuine terrestrial HA such as the cold or the exercise burden. The reported literature has tended to focus on the effects of HA on brachial artery BP and largely following a relatively short period brief ($\leq$6 hours) of simulated hypoxia.[22,26] Available data at terrestrial HA has shown that HA exposure typically leads to an increase in both resting systolic and 24 hour blood pressure which may be more pronounced in those with background hypertension.[9] The effects of HA on central BP and arterial stiffness have been barely examined at HA, yet they are well recognised to be better predictors of cardiovascular risk than brachial BP.[10,11] Given the vast numbers of patients with known hypertension and cardiovascular disease who undergo recreational HA exposure annually the ability to better define cardiovascular risk in these individuals would be important. This has added importance given that cardiovascular death is a leading cause of non-traumatic death at HA.[1] An improved understanding of the effects of HA on central BP and other non-invasive measures of cardiovascular risk such as arterial stiffness might allow for tailored medical therapy at HA to reduce the cardiovascular risk to individuals. We observed a significant increase in brachial but not central pulse pressure suggesting differences in BP behaviour in the peripheral versus the central circulation. Indeed whilst the brachial SBP was higher than that observed centrally the increase in central SBP was greater and was significant across all three altitudes studied (table 2).

There has only been one previous study to investigate the effects of HA on measures of both arterial stiffness and central BP at terrestrial altitude. Parati et al studied 44 subjects who were randomised to placebo or to oral acetazolamide prior to and during HA exposure.[8] Following sea level assessment the subjects ascended to 4559m within 28 hours by road to 1130m, then cable car to 3647m before completing the rest of the ascent on foot. Measurements at HA were obtained within 4-6 hours of arrival at 4559m and again after two days at this altitude. They observed a non-significant increase in both central and peripheral SBP but an even greater and significant increase in DBP. AI@75 significantly increased from Sea level to HA. However, whereas the SBP continued to increase from 4-6 hours to two days at HA there was no further increase in the AI@75 beyond the early increase. In our study we noted a similar sized increase in both brachial and central SBP to that in this previous study and the significance in our current study likely relate to our much larger sample size. Our data would seem to suggest that the increase in heart rate is a significant independent predictor of the increase in AI at HA which was not directly related to either the SpO_2 or altitude. The observed increase in heart rate, AI, brachial and central SBP would strongly suggest that these increases relate to sustained sympathetic activation at HA as has been well described rather than a genuine increase in large artery stiffness.[23]

In one of the only previously published studies to assess the effects of HA on arterial stiffness and brachial BP during a conventional trek Rhodes et al studied 17 subjects over an ascent from 80m to 4770m over 11 days.[6] They found that HA led to a transient increase in large artery stiffness index (using finger photoplethysmography) noted at day four at 3450 m before returning to baseline levels. A significant rise in both systolic and diastolic BP were observed at 3450m and the increase was sustained throughout the HA exposure.[6] Interestingly, they observed that the increase in BP was not related to changes in arterial stiffness nor was there a link between the increase in arterial tone and the presence of AMS. We did not identify a relationship between LLS, SpO2 and either AI, which is an indirect measure of large artery stiffness and central systolic BP at HA.

Consistent with previous research we found that the AI related to the subjects age and inversely correlated with height and heart rate.[27,28] This is explained by the fact that the time of the reflected wave is related to the dimensions of the body and heart rate. In shorter individuals, a reduced return time for reflected waves leads to an increase in central pressure augmentation.[27] As a result of the noted influence of heart rate on AI it has been suggested that AI should be adjusted for the effects of heart rate and this has traditionally been to an average of 75 per minute (AI@75).[29] Adjusting the AI@75 to account for heart rate did not alter our findings. It has also been more recently suggested that adjusting for heart rate on multivariate analysis of AI is more appropriate and this has been additionally done in our analysis.[30] Our data has shown that heart rate was the independent variable with the greatest impact on AI. Indeed augmentation of central BP is influenced by heart rate and therefore the duration of systole and shifting the reflected arterial wave to diastole and reducing the time to wave reflection as has been observed in our study.[29] Therefore it is reasonable to assume that the increase in AI at HA is largely related to the associated increase in heart rate leading to a rise in arterial augmentation and central BP rather than actual changes in large artery stiffness over only 14 days HA exposure.

In this study we were also interested in the effects of HA on the ssPPV. This is a measure of the variation in the pulse pressure averaged over the 10 second arterial waveform recording using the BP+ device. The beat to beat variation in pulse pressure is known be influenced by a number of factors including left ventricular preload, stroke volume and ventilation, which are all known to be affected at HA.[22] Clinically, probably the most widespread use of ssPPV has been to assess fluid responsiveness in mechanically ventilated patients intra-operatively and on intensive care.[20,21] During inspiration negative intrathoracic pressure leads to an increase in venous return and ultimately an increase in ventricular filling. Its effect on left ventricular stroke volume is influenced by hydration and intravascular filling, which is dependent on the relative position on the Frank-Starling curve.[19]HA-related hypoxia has been shown to affect both right and left ventricular stroke volume with variable effects on ventricular filling.[4.22.25] The mechanisms to explain these changes are complex and include the known hypoxia mediated pulmonary vasoconstriction leading to an increase in pulmonary artery systolic pressure and right ventricular afterload.[5] HA acclimatisation is known to lead to relative dehydration and hypoxia-mediated hyperventilation all of which may affect biventriuclar ventricular stroke volume. Whilst the ssPPV cannot be used in isolation serial measurements can be used to assess filling and fluid responsiveness. In our study the ssPPV was very susceptible to the effects of HA exposure but was not related to LLS. HA led to a marked increase in the ssPPV, despite no significant increase in the central arterial pulse pressure.

This study has a number of limitations that require acknowledgement. The subjects were studied in groups two days apart. This was done to accommodate the large sample size of the study and ensure excellent reproducibility of the measures and ensure that subject BP measurements were conducted robustly at each individual research station by trained researchers. The environmental factors, such as temperature and barometric pressure would not have been identical for the study groups at the time of their data collection which could have potentially influenced the findings. However, we did not observe any significant influence of the trekking group order of study on either AI or central systolic blood pressure. Unfortunately, we did not measure hormonal markers of sympathetic activation, such as circulating catecholamines, to better investigate the mechanism for the increase in SBP and AI, however, we did note that the increases did not relate to the degree of hypoxia (SpO_2) or LLS.

In conclusion in this study we found that HA exposure led to an increase in brachial and central SBP and a rise in AI compared with near sea level baseline levels. The increase in central SBP and AI was not related to the degree of hypoxia and SpO_2 at HA nor to LLS. The observed changes likely relate to increased sympathetic activation rather than any genuine change in large artery stiffness.

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Conflict of Interest

The authors have no conflict of interest to declare.

What is known about the topic?

- HA exposure leads to an increase in heart rate and there is evidence from a single study of rapid largely cable car ascent to 4559m that it leads to an increase in central SBP and arterial AI.

What this study adds?

- This is the first study to examine the effects of stepwise increasing terrestrial HA on arterial stiffness and central BP over a conventional and progressive HA trek to >5000m.
- We have discovered that the HA exposure led to a significant increase in central SBP and AI.
- Neither altitude nor the SpO_2 were independent predictors of AI and central SBP.
- The increase in AI related to the increase in heart rate at HA and did not reflect a genuine change in large artery stiffness.

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Legends for Figures

Figure 1 Ascent Profile the altitude and timing of data collection

Figure 2 Changes in systolic blood pressure with HA exposure. Symbol* denotes significant difference vs baseline level

Figure 3 Change in Augmentation Index with high altitude

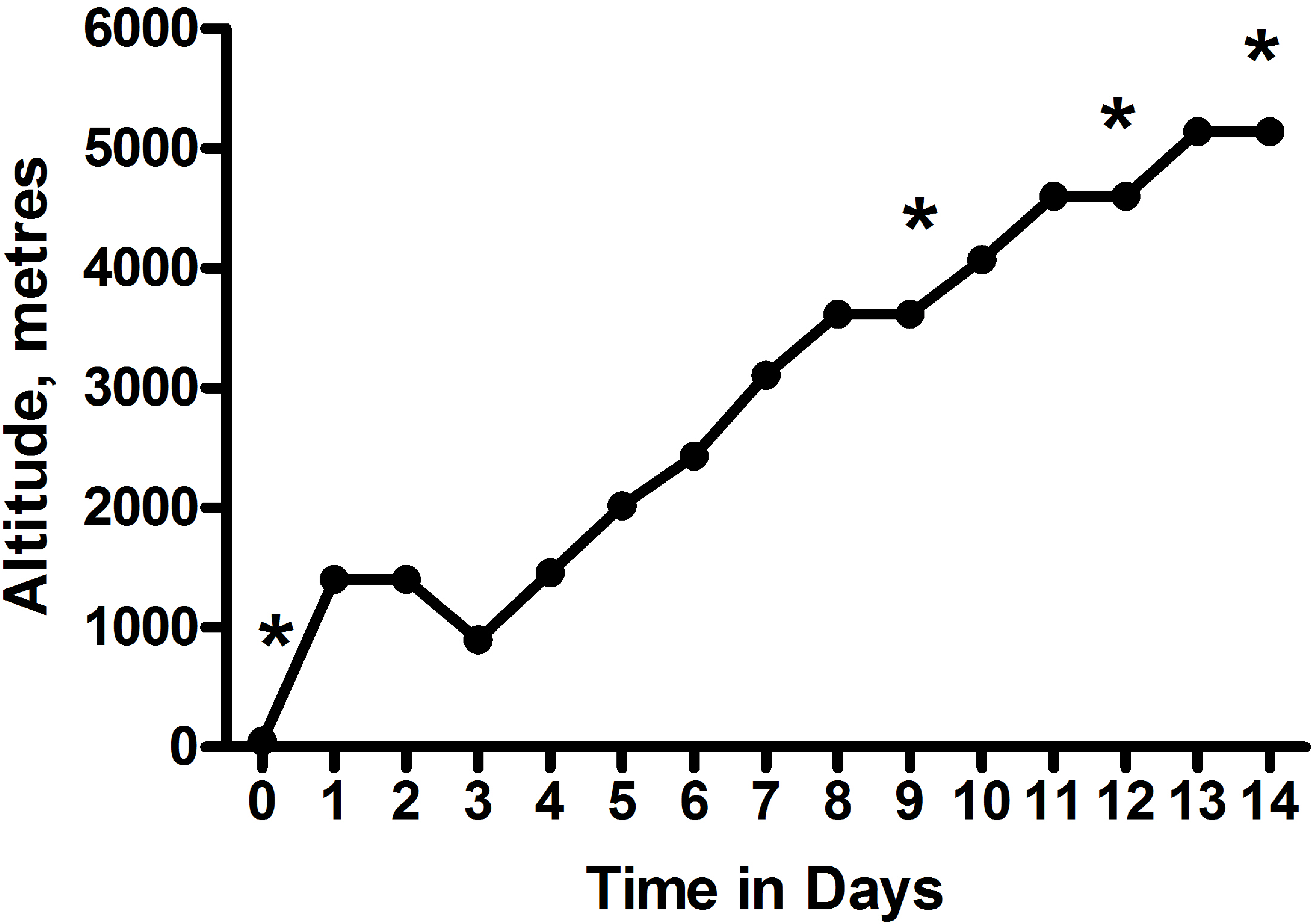
Table 1: Baseline Demographics

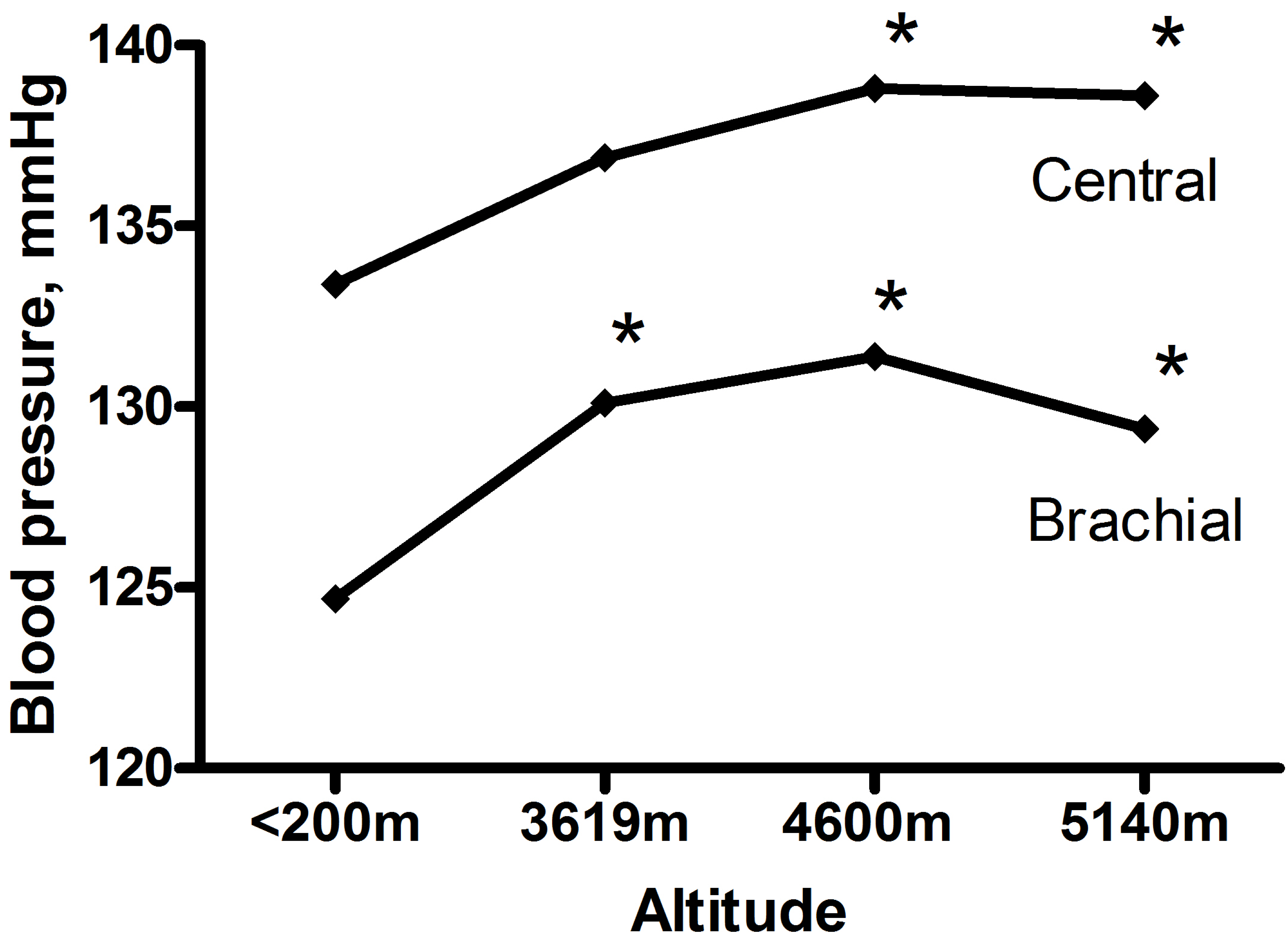
Demographic	Result
Age, years (range)	32.2±8.7 (18-56)
Males n, %	63 (70%)
Height, cm	173.5±9.1
weight	73.4±12.3
Body mass index kg/m^2	24.38±2.7
Ethnicity, %	
- Caucasian	87.8%
- Nepalese	11.1%
- South Asian	11.1%
Smoking status (N, %)	
- Current	9.3%
- Ex	12.3%
- Never	78.4%

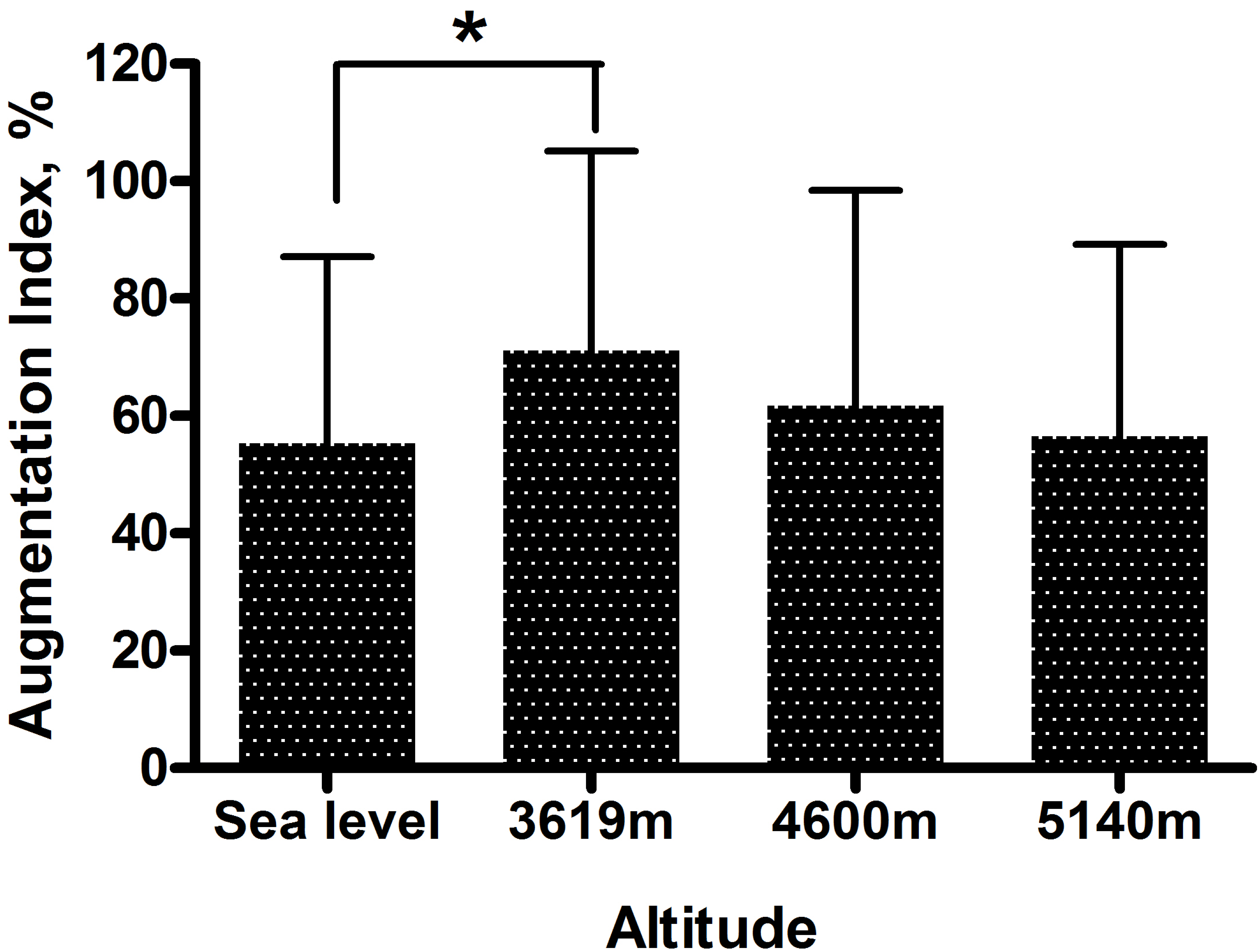
Table 2 Effect of high altitude on measured vascular parameters including central blood pressure and augmentation index

Parameter	Sea level	3619m	4600m	5140m	P value
Heart rate	65.2±12.8	69.6±11.8	77.3±15.3	78.2±13.6	<0.0001abc
Oxygen Saturations	97.7±1.4†	91.9±3.4	82.8±6.3	80.4±5.3	<0.0001abc
Lake louis Scores	0.23 (0.64)	1.1 (1.9)	1.4 (1.6)	1.3 (1.4)	<0.0001abc
Brachial artery systolic BP	132.8±14.0	136.9±13.4	138.8±13.3	138.6±13.9	0.04bc
Brachial artery diastolic BP	81.8±11.7	84.7±9.4	83.7±9.8	83.9±9.7	0.28
Mean brachial arterial BP	99.3±12.9	102.0±9.9	102.1±9.9	102.2±9.8	0.23
Brachial artery Pulse pressure	51.6±11.3	52.1±9.7	55.5±10.9	54.7±11.3	0.02b
Central systolic BP	124.7±14.8	130.1±14.2	131.4±15.4	129.4±14.3	0.02abc
Central arterial diastolic BP	84.0±11.6	87.5±9.6	86.8±9.6	87.3±9.5	0.09
Central artery pulse pressure	40.7±9.5	42.6±9.6	44.6±13.4	42.1±9.9	0.26
Augmentation index, %	55.3±34.9	71.1±34.1	61.8±36.7	56.6±32.7	0.001b
Reflected wave transit time, s	0.16±0.02	0.16±0.02	0.14±0.02	0.14±0.01	<0.0001bc
Systolic ejection period, s	0.30±0.03	0.31±0.02	0.29±0.03	0.28±0.02	<0.0001bc
Supra Systolic pulse pressure variation	0.23±0.13	0.28±0.15	0.37±0.20	0.34±0.19	<0.0001abc

BP, blood pressure; results of post hoc tests vs baseline sea level, a 3880m, b 4400m, c 5140m


6000
5000
4000
3000
2000
1000
0
Altitude, metres
*
*
*
*
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Time in Days


140
135
130
125
120
Blood pressure, mmHg
Central
Brachial
*
<200m
3619m
4600m
5140m
Altitude


*
120
100
80
60
40
20
0
Augmentation Index, %
Sea level
3619m
4600m
5140m
Altitude