

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

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

25 Ninety healthy adults were included. Central BP and the augmentation index (AI) were  
26 measured at the level of the brachial artery (Uscom BP+ device) at <200m and at 3619m,  
27 4600m and 5140m. The average age of the subjects (70% men) were  $32.2 \pm 8.7$  years.  
28 Compared with central arterial pressures, brachial SBP ( $+8.1 \pm 6.4$  mmHg;  $p < 0.0001$ ) and  
29 pulse pressure ( $+10.9 \pm 6.6$  mmHg;  $p < 0.0001$ ) were significantly higher and brachial DBP  
30 was lower ( $-2.8 \pm 1.6$  mmHg;  $P < 0.0001$ ). Compared <200m, HA led to a significant  
31 increase in brachial and central SBP. Central SBP correlated with AI ( $r = 0.50$ ; 95% CI:  
32 0.41 to 0.58;  $p < 0.0001$ ) and age ( $r = 0.32$ ; 21 to 0.41;  $p < 0.001$ ). AI positively correlated with  
33 age ( $r = 0.39$ ;  $p < 0.001$ ) and inversely with subject height ( $r = -0.22$ ;  $p < 0.0001$ ) weight ( $r = -$   
34 0.19;  $p = 0.006$ ) and heart rate ( $r = -0.49$ ;  $p < 0.0001$ ). There was no relationship between  
35 acute mountain sickness scores (LLS) and AI or central BP. The independent predictors of  
36 central SBP were male sex (coefficient,  $t = 4.7$ ;  $P < 0.0001$ ), age ( $t = 3.6$ ;  $p = 0.004$ ) and AI  
37 ( $t = 7.5$ ;  $p < 0.0001$ ; overall  $r^2 = 0.40$ ;  $p < 0.0001$ ). Subject height ( $t = 2.4$ ;  $p = 0.02$ ), age ( $t = 7.4$ ;  
38  $p < 0.0001$ ) and heart rate ( $t = 11.4$ ;  $P < 0.0001$ ) were the only independent predictors of AI  
39 (overall  $r^2 = 0.43$ ;  $p < 0.0001$ ). Central BP and AI significantly increase at HA. This rise was  
40 influenced by subject-related factors and heart rate but not independently by altitude, LLS  
41 or SpO<sub>2</sub>.

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43

## 44 **Introduction**

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

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

63 Unfortunately, the accurate non-invasive assessment of central BP and large artery  
64 stiffness has been traditionally very difficult. It had required the need for either arterial  
65 catheterisation or less portable and expensive non-invasive equipment limiting its research  
66 utility at HA, explaining the paucity of published research at genuine terrestrial HA.<sup>5,7</sup>

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

73 The Uscom BP<sup>+</sup> is a novel device which is able to estimate central blood pressure  
74 using a simple oscillometric BP cuff on the upper arm.<sup>12</sup> It has shown excellent agreement  
75 with catheter based assessments of central BP and gold standard measures of arterial  
76 stiffness.<sup>13,15</sup> It utilises pulse wave analysis to assess the AI which reflects the enhancement  
77 (augmentation) of central aortic systolic pressure by reflected arterial pulse waves. It has  
78 the advantage over several competing devices. It is highly portable and only requires the  
79 use of an upper arm cuff therefore avoiding the need to assess either the radial or digital  
80 pulse where the signal to noise ratio may be less favourable.

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

84

## 85 **Methods**

### 86 **Study design and participants**

87 Ninety healthy British Military servicemen aged >18years were included. Inclusion was  
88 entirely voluntary and represented a large subset of military servicemen who had been  
89 selected to take part in a quadrennial military adventure training exercise to HA.  
90 Significant mountaineering experience was not essential but those with very limited  
91 experience were encouraged to attend a winter skills course (<1200m) within 3 months of  
92 departure. The subjects were assessed at near sea level (<200m) and during progressive  
93 ascent in the Dhaulagiri region in the Himalayas in March/April 2016. Health status was  
94 confirmed following a detailed baseline questionnaire. All subjects were assessed to be  
95 medically fit for a high altitude venture by their general practitioner. To be considered fit  
96 they were all required to have passed their annual military basic fitness test which includes  
97 a 1.5 mile timed run. Key exclusion criteria included a history of hypertension and/ or  
98 atrial fibrillation. All participants were low altitude dwellers and none had prior exposure  
99 to >1400m terrestrial altitude in the four weeks prior to this study. The subjects were  
100 studied consecutively in groups of 8-10 individuals with a two day stagger between  
101 successive groups. HA related symptoms were assessed using the Lake Louis Scoring  
102 System (LLS).<sup>16,17</sup>

103

### 104 **High Altitude Ascent and descent profile**

105 The subjects flew from the UK to Kathmandu (1400m day 1-3) where they underwent a  
106 short period of local acclimatisation at 1400m. From there they travelled by a staged road  
107 move to Darbang (1030m) then on foot with loads of up to 12kg over the ensuing 11 days  
108 to HA of 5140m (after passing over French pas at 5360m) (figure 1). From there they

109 commenced trekking on foot over the ensuing 11 days (to day 14) to an altitude of 5140m  
110 (with an overpass of 5360m) before commencing their decent (day 15) on foot to Marpha  
111 (2719m) and then by road back to Kathmandu. Research assessments were performed at  
112 sea level and at static research camps at 3619m (day 9), 4600m (day 12) and 5140m (day  
113 14) during ascent.

114

### 115 **Physiological assessments and central blood pressure measurement**

116 Oxygen saturations (SpO<sub>2</sub>) were measured using a Nonin Onyx (Nonin Medical Inc,  
117 Plymouth, Minnesota, USA) pulse oximeter. Blood pressure and arterial stiffness  
118 assessments were obtained at the same time using an Uscom BP<sup>+</sup> device (Uscom, Sydney,  
119 NSW, Australia) as previously reported.<sup>13-15</sup> The upper arm cuff was attached to the  
120 dominant arm of seated subjects. All subjects were rested for at least five minutes prior to  
121 BP assessment and they were not permitted to drink caffeine or smoke for at least three  
122 hours and alcohol for  $\geq 10$  hours prior to BP measurements.<sup>18</sup> The subjects were advised  
123 not to speak during the recordings. The BP<sup>+</sup> device measures both central and peripheral  
124 BP (mmHg) using supra systolic oscillometry. Following an initial inflation-deflation the  
125 cuff is re-inflated to approximately  $\geq 30$ mm Hg above the recorded suprasystolic pressure  
126 for 10 seconds, during which suprasystolic BP and pulse wave assessments are recorded  
127 via the arm cuff. All recordings were stored on a mini SD card within the device and later  
128 exported for data analysis. Only readings with a signal-to-noise ratio of  $\geq 6$  were  
129 included and tests with a ratio of  $< 6$  were repeated.

130 The BP<sup>+</sup> calculates a number of additional haemodynamic indices that were of  
131 interest to this study, including the AI. Its quoted AI is the arterial augmentation pressure  
132 (difference between the second and first systolic peaks of the central pressure waveform)

133 expressed as a percentage of the pulse pressure and it is an *indirect* measure of large  
134 arterial stiffness. Further parameters that we were specifically interested in for this study  
135 were the time to systolic wave Reflection (TR) and the suprasystolic pulse pressure  
136 variation (ssPPV). The reflected Wave Transit Time is an indirect measure of pulse wave  
137 velocity and large arterial stiffness. The ssPPV is a novel measure of fluid responsiveness  
138 and is heavily influenced by respiratory variation and left ventricular stroke volume, both  
139 of which can be affected at HA.<sup>19-21</sup> The BP<sup>+</sup> calculates the ssPPV as the difference  
140 between maximum and minimum pulse pressures divided by the average pulse pressure  
141 over the 10 second rhythm strip.

142

#### 143 **Ethics**

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

148

#### 149 **Statistical analysis**

150 Data were analysed using GraphPad InStat version 3.05 and with all graphical figures  
151 presented using GraphPad Prism version 4.00 for Windows (GraphPad Software, San  
152 Diego, CA, USA). Sample size calculations were performed using a proprietary  
153 determined sample- size calculator using (GraphPad StatMate version 2.00 for Windows).  
154 The Kolmogorov-Smirnov test was undertaken to assess normality of all continuous data  
155 and all continuous data are presented as mean  $\pm$  standard deviations and median  $\pm$

156 interquartile range for parametric and non-parametric data respectively. Comparison of  
157 unpaired data was performed using an unpaired T test or the Mann-Whitney Test for  
158 parametric and non-parametric data respectively and with a paired t test and Wilcoxon  
159 matched pairs test for equivalent paired data. Continuous data from  $\geq 3$  groups were  
160 compared using a one-way Analysis of Variance (ANOVA) with either Tukey post-hoc  
161 tests or a Kruskal-Wallis test with Dunn post-test for parametric and non-parametric data  
162 respectively. Correlations were performed using Pearson and Spearman rank correlation  
163 ( $\pm 95\%$  confidence interval, CI) for parametric and non-parametric data respectively. A  
164 two tailed  $P$  value  $< 0.05$  was considered statistically significant for all comparisons. All  
165 univariate predictors of central arterial systolic blood pressure were entered into a multiple  
166 linear regression analysis model in order to identify its independent predictors. A two  
167 tailed  $P$  value  $< 0.05$  was considered statistically significant for all comparisons.

#### 168 **Sample size calculations**

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

178

#### 179 **Results**



180 Ninety subjects were included. The average age of the subjects were  $32.2 \pm 8.7$  years with  
181 70% being male. Heart rate and LLS increased and  $SpO_2$  fell at HA compared with sea  
182 level (table 1). The average 1.5 mile run time for included subjects was  $9.9 \pm 1.2$  minutes.

183 Overall brachial arterial SBP ( $+8.4$  [5.0 to 12.0] mmHg;  $p < 0.0001$ ) and pulse  
184 pressure ( $+11$  [7.0 to 15.0] mmHg;  $p < 0.0001$ ) were significantly greater than that observed  
185 centrally. Conversely the brachial artery DBP was lower ( $-2.6$  [-3.4 to -2.0] mmHg;  
186  $P < 0.0001$ ) than the equivalent central readings.

187 Compared with baseline sea level values there was a significant increase in both  
188 brachial and central SBP and in brachial but not central arterial pulse pressure at HA (table  
189 2). The highest increase in both brachial and central SBP was between sea level and 4619m  
190 ( $+7.0$  [-5.0 to 16.0] and  $+7.0$  [-4.5 to 18.0] mmHg respectively) (table 2; figure 2).

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

194 There were significant correlations between central SBP and both AI ( $r = 0.50$ ; 0.41  
195 to 0.58;  $p < 0.0001$ ) and age ( $r = 0.32$ ; 21 to 0.41;  $p < 0.001$ ). Other independent, albeit weak  
196 predictors, of central SBP were  $SpO_2$  ( $r = -0.14$  -0.25 to -0.05;  $p = 0.02$ ), heart rate ( $r = -0.16$ ;  
197 -0.27 to -0.05;  $p = 0.003$ ) male sex ( $r = 0.15$ ; 0.04 to 0.26;  $p = 0.004$ ) ethnicity ( $r = 0.15$ ; 0.04 to  
198 0.25;  $p = 0.007$ ) smoking status ( $r = 0.18$ ; -0.28 to -0.07;  $p = 0.001$ ) and altitude ( $r = 0.10$ ;  
199  $p = 0.05$ ). AI positively correlated with age ( $r = 0.39$ ;  $p < 0.001$ ) and inversely with subject  
200 height ( $r = -0.22$ ;  $p < 0.0001$ ) weight ( $r = -0.19$ ;  $p = 0.006$ ), and heart rate ( $r = -0.49$ ;  $p < 0.0001$ ). There  
201 was no relationship between LLS and either AI or central BP.

202 Multivariate analysis was performed to assess the independent predictors of central  
203 systolic BP. Only the univariate predictors were included in the model. The independent

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

211

## 212 **Discussion**

213 To the author's knowledge, this is the first study to assess the effects of stepwise increasing  
214 terrestrial HA on arterial stiffness and central BP over a conventional and progressive HA  
215 trek. We found that HA exposure led to a significant increase in central SBP and AI.  
216 Neither altitude nor the SpO<sub>2</sub> were independent predictors of AI and central SBP. Heart  
217 rate was a significant determinant of both AI and central BP.

218 HA exposure leads to a wide range of complex effects on both the pulmonary and  
219 systolic circulation which have been well described.<sup>2,4,5,22</sup> Hypobaric hypoxia leads to  
220 widespread sympathetic activation leading to an increase in resting heart rate.<sup>23-25</sup> The  
221 reported effects on BP are variable and are highly dependent on the degree of hypoxia and  
222 speed and duration of exposure. Furthermore, the type of hypoxic environment may be a  
223 major confounder.<sup>26</sup> Several previously published studies have used simulated hypoxia  
224 (using either a normobaric or hypobaric chamber) in an attempt to replicate the degree of  
225 hypoxia observed at genuine HA.<sup>4,22,25,26</sup> Whilst they are very useful surrogates for HA  
226 exposure, u simulated hypoxia does not fully reproduce the environmental and  
227 geographical effects genuine terrestrial HA such as the cold or the exercise burden. The

228 reported literature has tended to focus on the effects of HA on brachial artery BP and  
229 largely following a relatively short period brief ( $\leq 6$  hours) of simulated hypoxia.<sup>22,26</sup>  
230 Available data at terrestrial HA has shown that HA exposure typically leads to an increase  
231 in both resting systolic and 24 hour blood pressure which may be more pronounced in  
232 those with background hypertension.<sup>9</sup> The effects of HA on central BP and arterial  
233 stiffness have been barely examined at HA, yet they are well recognised to be better  
234 predictors of cardiovascular risk than brachial BP.<sup>10,11</sup> Given the vast numbers of patients  
235 with known hypertension and cardiovascular disease who undergo recreational HA  
236 exposure annually the ability to better define cardiovascular risk in these individuals would  
237 be important. This has added importance given that cardiovascular death is a leading cause  
238 of non-traumatic death at HA.<sup>1</sup> An improved understanding of the effects of HA on central  
239 BP and other non-invasive measures of cardiovascular risk such as arterial stiffness might  
240 allow for tailored medical therapy at HA to reduce the cardiovascular risk to individuals.  
241 We observed a significant increase in brachial but not central pulse pressure suggesting  
242 differences in BP behaviour in the peripheral versus the central circulation. Indeed whilst  
243 the brachial SBP was higher than that observed centrally the increase in central SBP was  
244 greater and was significant across all three altitudes studied (table 2).

245         There has only been one previous study to investigate the effects of HA on  
246 measures of both arterial stiffness and central BP at terrestrial altitude. Parati et al studied  
247 44 subjects who were randomised to placebo or to oral acetazolamide prior to and during  
248 HA exposure.<sup>8</sup> Following sea level assessment the subjects ascended to 4559m within 28  
249 hours by road to 1130m, then cable car to 3647m before completing the rest of the ascent  
250 on foot. Measurements at HA were obtained within 4-6 hours of arrival at 4559m and  
251 again after two days at this altitude. They observed a non-significant increase in both  
252 central and peripheral SBP but an even greater and significant increase in DBP. AI@75

253 significantly increased from Sea level to HA. However, whereas the SBP continued to  
254 increase from 4-6 hours to two days at HA there was no further increase in the AI@75  
255 beyond the early increase. In our study we noted a similar sized increase in both brachial  
256 and central SBP to that in this previous study and the significance in our current study  
257 likely relate to our much larger sample size. Our data would seem to suggest that the  
258 increase in heart rate is a significant independent predictor of the increase in AI at HA  
259 which was not directly related to either the SpO<sub>2</sub> or altitude. The observed increase in heart  
260 rate, AI, brachial and central SBP would strongly suggest that these increases relate to  
261 sustained sympathetic activation at HA as has been well described rather than a genuine  
262 increase in large artery stiffness.<sup>23</sup>

263           In one of the only previously published studies to assess the effects of HA on  
264 arterial stiffness and brachial BP during a conventional trek Rhodes et al studied 17  
265 subjects over an ascent from 80m to 4770m over 11 days.<sup>6</sup> They found that HA led to a  
266 transient increase in large artery stiffness index (using finger photoplethysmography) noted  
267 at day four at 3450 m before returning to baseline levels. A significant rise in both systolic  
268 and diastolic BP were observed at 3450m and the increase was sustained throughout the  
269 HA exposure.<sup>6</sup> Interestingly, they observed that the increase in BP was not related to  
270 changes in arterial stiffness nor was there a link between the increase in arterial tone and  
271 the presence of AMS. We did not identify a relationship between LLS, SpO<sub>2</sub> and either AI,  
272 which is an indirect measure of large artery stiffness and central systolic BP at HA.

273           Consistent with previous research we found that the AI related to the  
274 subjects age and inversely correlated with height and heart rate.<sup>27,28</sup> This is explained by  
275 the fact that the time of the reflected wave is related to the dimensions of the body and  
276 heart rate. In shorter individuals, a reduced return time for reflected waves leads to an  
277 increase in central pressure augmentation.<sup>27</sup> As a result of the noted influence of heart rate

278 on AI it has been suggested that AI should be adjusted for the effects of heart rate and this  
279 has traditionally been to an average of 75 per minute (AI@75).<sup>29</sup> Adjusting the AI@75 to  
280 account for heart rate did not alter our findings. It has also been more recently suggested  
281 that adjusting for heart rate on multivariate analysis of AI is more appropriate and this has  
282 been additionally done in our analysis.<sup>30</sup> Our data has shown that heart rate was the  
283 independent variable with the greatest impact on AI. Indeed augmentation of central BP is  
284 influenced by heart rate and therefore the duration of systole and shifting the reflected  
285 arterial wave to diastole and reducing the time to wave reflection as has been observed in  
286 our study.<sup>29</sup> Therefore it is reasonable to assume that the increase in AI at HA is largely  
287 related to the associated increase in heart rate leading to a rise in arterial augmentation and  
288 central BP rather than actual changes in large artery stiffness over only 14 days HA  
289 exposure.

290 In this study we were also interested in the effects of HA on the ssPPV. This is a  
291 measure of the variation in the pulse pressure averaged over the 10 second arterial  
292 waveform recording using the BP<sup>+</sup> device. The beat to beat variation in pulse pressure is  
293 known be influenced by a number of factors including left ventricular preload, stroke  
294 volume and ventilation, which are all known to be affected at HA.<sup>22</sup> Clinically, probably  
295 the most widespread use of ssPPV has been to assess fluid responsiveness in mechanically  
296 ventilated patients intra-operatively and on intensive care.<sup>20,21</sup> During inspiration negative  
297 intrathoracic pressure leads to an increase in venous return and ultimately an increase in  
298 ventricular filling. Its effect on left ventricular stroke volume is influenced by hydration  
299 and intravascular filling, which is dependent on the relative position on the Frank-Starling  
300 curve.<sup>19</sup> HA-related hypoxia has been shown to affect both right and left ventricular stroke  
301 volume with variable effects on ventricular filling.<sup>4,22,25</sup> The mechanisms to explain these  
302 changes are complex and include the known hypoxia mediated pulmonary vasoconstriction

303 leading to an increase in pulmonary artery systolic pressure and right ventricular afterload.<sup>5</sup>  
304 HA acclimatisation is known to lead to relative dehydration and hypoxia-mediated  
305 hyperventilation all of which may affect biventricular stroke volume. Whilst  
306 the ssPPV cannot be used in isolation serial measurements can be used to assess filling and  
307 fluid responsiveness. In our study the ssPPV was very susceptible to the effects of HA  
308 exposure but was not related to LLS. HA led to a marked increase in the ssPPV, despite no  
309 significant increase in the central arterial pulse pressure.

310         This study has a number of limitations that require acknowledgement. The subjects  
311 were studied in groups two days apart. This was done to accommodate the large sample  
312 size of the study and ensure excellent reproducibility of the measures and ensure that  
313 subject BP measurements were conducted robustly at each individual research station by  
314 trained researchers. The environmental factors, such as temperature and barometric  
315 pressure would not have been identical for the study groups at the time of their data  
316 collection which could have potentially influenced the findings. However, we did not  
317 observe any significant influence of the trekking group order of study on either AI or  
318 central systolic blood pressure. Unfortunately, we did not measure hormonal markers of  
319 sympathetic activation, such as circulating catecholamines, to better investigate the  
320 mechanism for the increase in SBP and AI, however, we did note that the increases did not  
321 relate to the degree of hypoxia (SpO<sub>2</sub>) or LLS.

322

323 In conclusion in this study we found that HA exposure led to an increase in brachial and  
324 central SBP and a rise in AI compared with near sea level baseline levels. The increase in  
325 central SBP and AI was not related to the degree of hypoxia and SpO<sub>2</sub> at HA nor to LLS.

326 The observed changes likely relate to increased sympathetic activation rather than any  
327 genuine change in large artery stiffness.

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329

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332 Cardiology at Poole Hospital for their support. We are extremely grateful to the subjects  
333 for their time and for volunteering to take part in this study.

334

### 335 **Conflict of Interest**

336 The authors have no conflict of interest to declare.

337

338 *What is known about the topic?*

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

342

343 *What this study adds?*

- 344 ● This is the first study to examine the effects of stepwise increasing terrestrial HA on  
345 arterial stiffness and central BP over a conventional and progressive HA trek to  
346 >5000m.
- 347 ● We have discovered that the HA exposure led to a significant increase in central SBP  
348 and AI.
- 349 ● Neither altitude nor the SpO<sub>2</sub> were independent predictors of AI and central SBP.

350 • The increase in AI related to the increase in heart rate at HA and did not reflect a  
351 genuine change in large artery stiffness.

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447 **Legends for Figures**

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449 **Figure 1** Ascent Profile the altitude and timing of data collection

450 **Figure 2** Changes in systolic blood pressure with HA exposure. Symbol\* denotes

451 significant difference vs baseline level

452 **Figure 3** Change in Augmentation Index with high altitude

**Table 1: Baseline Demographics**

<b>Demographic</b>	<b>Result</b>
Age, years (range)	32.2±8.7 (18-56)
Males n, %	63 (70%)
Height, cm	173.5±9.1
Weight, kg	73.4±12.3
Body mass index kg/m <sup>2</sup>	24.38±2.7
Ethnicity, %	
- Caucasian	78 (86.7%)
- Nepalese	11 (12.2%)
- South Asian	1 (1.1%)
Smoking status (N, %)	
- Current	9 (10%)
- Ex	11 (12.2%)
- Never	70 (77.8%)

**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/ minute	65.2±12.8	69.6±11.8	77.3±15.3	78.2±13.6	<0.0001*†‡
Oxygen Saturations, %	97.7±1.4†	91.9±3.4	82.8±6.3	80.4±5.3	<0.0001*†‡
Lake louis Scores	0.23 (0.64)	1.1 (1.9)	1.4 (1.6)	1.3 (1.4)	<0.0001*†‡
Brachial artery systolic BP, mmHg	132.8±14.0	136.9±13.4	138.8±13.3	138.6±13.9	0.04†‡
Brachial artery diastolic BP, mmHg	81.8±11.7	84.7±9.4	83.7±9.8	83.9±9.7	0.28
Mean brachial arterial BP, mmHg	99.3±12.9	102.0±9.9	102.1±9.9	102.2±9.8	0.23
Brachial artery pulse pressure, mmHg	51.6±11.3	52.1±9.7	55.5±10.9	54.7±11.3	0.02†
Central systolic BP, mmHg	124.7±14.8	130.1±14.2	131.4±15.4	129.4±14.3	0.02*†‡
Central diastolic BP, mmHg	84.0±11.6	87.5±9.6	86.8±9.6	87.3±9.5	0.09
Central artery pulse pressure, mmHg	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	0.001†
Reflected wave transit time, s	0.16±0.02	0.16±0.02	0.14±0.02	0.14±0.01	<0.000*†‡
Systolic ejection period, s	0.30±0.03	0.31±0.02	0.29±0.03	0.28±0.02	<0.0001†‡
Supra Systolic pulse pressure variation	0.23±0.13	0.28±0.15	0.37±0.20	0.34±0.19	<0.0001*†‡
BP, blood pressure; results of post hoc tests vs baseline sea level, *3880m, † 4400m, ‡ 5140m					







