

BLOOD PRESSURE AND ALTITUDE: AN OBSERVATIONAL COHORT STUDY OF HYPERTENSIVE AND NON-HYPERTENSIVE HIMALAYAN TREKKERS IN NEPAL

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Details of Contributors

LK and BB conceived the idea and secured funding. LK, JS and SP designed the study. LK, TDS, LM, NR, BP, SP, JS, MM, DC, CD, TM, PP, AS, DT and DY participated in data collection and data analyses. TDS and LK wrote the first draft. All authors had full access to all of the data and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in revising and approving the final draft. LK is the guarantor.

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Abstract

Objectives: To determine how blood pressure (BP) changes with altitude in normotensive versus hypertensive trekkers. Secondary aims were to evaluate the prevalence of severe hypertension (BP $\geq 180/100$ mmHg), and efficacy of different antihypertensive agents at high altitude.

Methods: This was an observational cohort study of resting and 24-h ambulatory BP at 2860m, 3400m and 4300m in normotensive and hypertensive trekkers at 2860m, 3400m and 4300m in Nepal.

Results: We enrolled 672 trekkers age 18 years and older, 60 with a prior diagnosis of hypertension. Mean systolic BP was similar across altitudes in normotensive [127 mmHg (95% confidence interval 126 to 128 vs. 127 (126 to 129) vs 128 (95%CI 126 to 130), $p=NS$] and hypertensive trekkers [151 mmHg (145 to 156) vs. 150 (144 to 157) vs 144 (136 to 152), $p=NS$] as were mean diastolic pressures. However, there was large inter-individual variability. At 3400 m, the majority (60%, $n=284$) of normotensive subjects had a BP within 10mmHg of their BP at 2860 m while 21% ($n=102$) increased and 19% ($n=91$) decreased. The pattern was similar between 3400m and 4300m (65% ($n=202$) no change, 21% ($n=65$) increased, 15% ($n=46$) decreased). A greater proportion of hypertensive trekkers had a decrease in blood pressure at higher altitudes versus normotensives (36% ($n=15$) vs. 21% at 3400m, $p=0.01$ and 30% ($n=7$) vs. 15% at 4300m, $p=0.05$). Severe hypertension occurred in both groups, but was asymptomatic. It occurred most frequently in trekkers on angiotensin converting enzyme inhibitors or angiotensin receptor blockers, and not at all on those taking beta-blockers or thiazides. Nocturnal BP decreased in normotensive and increased in hypertensive trekkers.

Conclusions: Most travelers, including those with well controlled hypertension, can be reassured that their blood pressure will remain relatively stable at high altitude. Though extremely elevated blood pressure may be observed at high altitude in normotensive and hypertensive people, it is unlikely to be symptomatic. The ideal antihypertensive regimen at high altitude remains unclear.

Key words: blood pressure, hypertension, 24-h ambulatory blood pressure monitoring, high altitude, hypoxia, antihypertensive medication, Nepal

Introduction

Hypertension is the most common cardiovascular disease found in people recreating at high altitudes (Faulhaber, Flatz *et al.* 2007, Faulhaber, Flatz *et al.* 2007, Faulhaber, Gatterer *et al.* 2011). In healthy individuals without hypertension, blood pressure has been shown to increase, decrease, or not change depending on the study (reviewed in Luks (Luks 2009)) (Parati, Bilo *et al.* 2014). Similar variations have been observed in hypertensive subjects (Luks 2009, Bilo, Villafuerte *et al.* 2015), though case series have described patients whose blood pressure is well controlled at sea-level but consistently high when they are above 2000m (Bachman, Day *et al.* 2004, Handler 2009).

What to advise people with underlying hypertension traveling to high altitude remains unclear (Luks 2009). Rimoldi *et al.* have suggested pre-exposure ambulatory blood pressure monitoring for those with uncontrolled hypertension (Rimoldi, Sartori *et al.* 2010). These authors go as far as to state that ascent is absolutely contraindicated if arterial hypertension is poorly controlled ($\geq 160/100$ mmHg at rest or > 220 mmHg systolic upon exertion). However, we have found no reports of adverse outcomes related to uncontrolled hypertension at high altitude. In addition, little evidence exists to support the potential danger of asymptomatic, short-term, hypertension (Wolf, Lo *et al.* 2013, Patel, Young *et al.* 2016). The prevalence of severe hypertension (BP $\geq 180/100$ mmHg) at high altitude has not been well documented, and it is unknown whether blood pressure control becomes more difficult with ascent.

Prior studies on blood pressure at high altitude are limited in that most have been done below 3500m and have a small number (range 8-97 subjects) of homogenous participant pools (Vogel and Harris 1967, Hannon and Sudman 1973, Malhotra, Selvamurthy *et al.* 1976, Somers, Mark *et al.* 1988, Palatini, Businaro *et al.* 1989, Roach, Houston *et al.* 1995, Levine, Zuckerman *et al.* 1997, Luks 2009, Parati, Bilo *et al.* 2014, Bilo, Villafuerte *et al.* 2015). It is unknown whether the conclusions of these studies are applicable to a more general population of trekkers, or over a wider range of altitudes.

Evidence is also limited regarding the efficacy of antihypertensive medications at high altitude. Prior studies have examined the blood pressure lowering effects of beta-blockers and angiotensin receptor blockers (ARBs) in normotensive subjects at high altitude (Bilo, Caldara et al. 2011, Parati, Bilo et al. 2014), but only the combination of telmesartan and nifedipine has been examined in subjects with underlying hypertension (Bilo, Villafuerte et al. 2015).

We therefore asked how blood pressure changed with increasing altitudes in a large sample of trekkers in Nepal, and whether changes in blood pressure differed in those with underlying hypertension compared to those without. We hypothesized *a priori* that greater increases in blood pressure would be observed in trekkers with underlying hypertension than in those without hypertension. As secondary aims, we examined prevalence of severe hypertension, and the efficacy of different classes of antihypertensives in preventing severe hypertension at high altitude.

Methods

This study was a prospective observational cohort study comparing blood pressure in normotensive and hypertensive subjects at increasing altitudes in trekkers in the Solukhumbu Valley of Nepal. The Nepal Health Research Council Ethics Board approved this study.

Participants

Volunteer subjects were recruited in Lukla (2860m) from October 8, 2014 to November 2, 2015. Eligible subjects were trekkers and guides over 18 years of age. Subjects younger than 18 years, pregnant women, and those who declined to participate were excluded. Investigators approached trekkers arriving in Lukla to ask for their participation. If subjects agreed to participate, the informed consent process was completed. Subjects were assigned a number for anonymity and responded to a

questionnaire written in English or Nepali. Details of the questionnaire are described elsewhere (Keyes, Mather et al. 2016).

Outcome measures

Self-reported variables collected included age, height, weight, home country and city, smoking status, fitness level, home blood pressure (as a number or characterized as low, normal, or high), medical history, and medications.

Initial blood pressure and heart rate were measured and recorded on a standardized form for all study participants at within 24 hours of arrival at 2860m, 3400m and 4300m. Manual blood pressures were measured by stethoscope auscultation(Chobanian, Bakris et al. 2003) with Welch-Allyn sphygmomanometers in either the left or right arm. Aneroid sphygmomanometers such as these have been demonstrated to be accurate and unaffected by altitude(Kametas, McAuliffe et al. 2006).

Blood pressure measurement procedure was identical at each altitude. The subject remained seated with feet on the ground, comfortable and at rest for at least 5 minutes before measurements taken. The arm was fully exposed, with no layers of clothing beneath the blood pressure cuff. Measurements at 2860m were made indoors, in tea houses, typically between 8am-12pm. Pressures were measured in the same arm at all subsequent altitudes. In Namche Bazaar (3400m) measurements were made both indoors and outdoors between 2pm-6pm, and indoors between 2pm-7pm in either Pheriche or Dingboche (4300m). Most subjects subsequently ascended above 4300m. Measurements were taken at the same locations and hours several days later as subjects descended from their ultimate trekking destinations.

Subjects were directed to check in with the team at specific locations in each village. To minimize loss to follow up, investigators made rounds of lodges to locate enrolled subjects for assessment. Research assistants taking blood pressure were not aware of prior measurements.

We also recorded peripheral oxygen saturation, and Lake Louise Score (LLS) for acute mountain sickness (AMS). These results are reported separately (Starling, Keyes et al. 2016) and showed there was no relationship between blood pressure and AMS, and therefore these results should not impact the current analyses.

We defined severely elevated blood pressure as blood pressure of greater than or equal to $SBP \geq 180$ or $DBP > 100$ mmHg in accordance with JN7 definition of stage 2 hypertension that would require timely follow-up and treatment (Chobanian, Bakris et al. 2003, Wolf, Lo et al. 2013). If subjects had a measured blood pressure of greater than or equal to 180/100 mmHg at any checkpoint, they were assessed for signs and symptoms of hypertensive emergency and referred for medical evaluation if symptomatic (Wolf, Lo et al. 2013).

Ambulatory blood pressure monitoring (24h-ABPM) was performed in a sub-set of subjects using Welch-Allyn 6100 24h ambulatory BP monitors every 30 minutes while awake and every 60 minutes while asleep. ABPM was measured between 2860m-3440m and 3440m-4400m.

Statistical Analyses

We estimated that we would need at least 36 subjects in each group to detect a meaningful difference in blood pressure between those with hypertension based on a Cohen's value of 0.5. We aimed to recruit at least 60 trekkers with hypertension for anticipated loss to follow up when trekkers moved to subsequently higher locations.

Data were recorded on standardized paper data form and transferred to a Google spreadsheet and then into Microsoft Excel. Missing values were not included in calculations or analyses. Descriptive and summary statistics were calculated with Microsoft Excel and included all patients with relevant data

from each respective altitude. These are presented as mean (95% confidence interval (CI)) or frequency. Individual data is presented in figures to illustrate patterns and variability. We report descriptive and individual summary statistics for 24 ABPM data, but due to small number of participants, comparative statistics were not performed.

Comparisons between normotensive and hypertensive trekkers and between altitudes within groups were made with repeated measures ANOVA in subjects for whom there were complete data at all three altitudes.

We considered a change in blood pressure of greater than 10mmHg clinically relevant and calculated the number and percent of subjects who increased or decreased this amount between altitudes. Z-ratios were calculated to determine if difference in proportions between hypertensive and normotensive trekkers were significant. We used MedCalc version 16.2 for statistical analyses. A two-tailed p -value < 0.05 was considered significant.

Results

We enrolled a total of 672 trekkers (5 were enrolled at 3400m); of those 604 were normotensive, 60 had a prior diagnosis of hypertension, six who identified themselves as “borderline hypertensive”, and two who enrolled, but did not participate or complete the questionnaire. The latter eight were excluded from further analyses. The flow of subjects through the study at each location is shown in Figure 1.

Given the logistics of recruiting trekkers who were leaving the Lukla airport, on the trail, or in lodges and tea houses we cannot confirm how many were potentially eligible subjects were missed, or how many were approached but declined to participate. Details of the study population demographics are reported elsewhere (Keyes, Mather et al. 2016). Key demographic data and medical history is

compared between normotensive trekkers and hypertensive trekkers in Table 1. All but six subjects lived below 2500m; none of these six had hypertension.

About half of the subjects reported a numeric value for their usual home blood pressure (table 1). Mean systolic blood pressure was higher at 2860m compared to self-reported home blood pressure in both normotensive and hypertensive subjects who had documented values for both sites (table 1 and 2, $p<0.05$). However, in normotensive subjects, mean systolic and diastolic blood pressures were well within normal limits at 2860m.

Distribution of blood pressure values among individuals at each altitude is shown in Figure 2. In both normotensive and hypertensive subjects, there was no difference in mean systolic blood pressure between altitudes on ascent or descent (Table 2). Diastolic blood pressure was statistically higher at 3400m and 4300m compared to 2380m in normotensive subjects. At any given altitude, mean blood pressure was higher in those with hypertension compared to those without ($p<0.05$). Although mean systolic blood pressure values were similar at each altitude within groups, changes in blood pressure demonstrated large inter-individual variability (Figure 3).

At 3400m, the majority (60%, $n=284$) of normotensive trekkers had measurements within 10mmHg of their initial blood pressure at 2860m. Only 21% ($n=102$) had an increase greater than 10mmHg, and a nearly equal proportion, 19% ($n=91$), demonstrated a decrease of greater than 10mmHg. Results were similar between 3400m and 4300m (Figure 3) where no change was observed in 65% ($n=202$) of the normotensive trekkers, with an increase of at least 10 mmHg in 21% ($n=65$), and decrease of at least 10 mmHg in the remaining 15% ($n=46$).

Similar to normotensive subjects, blood pressure did not change with increasing altitude in most hypertensive trekkers (Figure 3). Between 2860m and 3400m pressure 45% ($n=19$) of the hypertensives had no change and 19% ($n=8$) increased. A greater proportion of hypertensive trekkers 36% ($n=15$) had

a decrease in systolic blood compared to normotensive trekkers ($p<0.05$). At the higher altitudes, compared to normotensive trekkers, a smaller proportion of hypertensive trekkers (44% ($n=10$)) had no change in systolic blood pressure, a similar proportion (26% ($n=6$)) increased, and greater proportion (30% ($n=7$)) decreased ($p<0.05$) (Figure 3).

Further highlighting the individual variability in blood pressure response to high altitude, the direction of change within subjects varied between altitudes. The direction of change between 2380m and 3400m and between 3400m and 4300m was the same in 61% of subjects ($n=204$), including those whose blood pressure stayed within 10mmHg of the first measurement at both higher altitudes; whereas the direction of change differed in 24% ($n=81$). The remaining 14% ($n=48$) of subjects had a change of greater than 10mmHg between the lower altitudes, but not between the higher altitudes.

Extreme blood pressures were observed in normotensive trekkers and hypertensive trekkers alike (Figure 4). Hypotension ($\leq 90/60$ mmHg) was documented in a small proportion of normotensives at each altitude on ascent and descent. None of these participants reported symptoms attributable to low blood pressure. Two (3%) trekkers with underlying hypertension had hypotension at 2860m. Only one was symptomatic and his case is reported elsewhere (Keyes, Mather et al. 2016). No hypertensive subjects had blood pressure $\leq 90/60$ mmHg at higher altitudes or on descent.

On the other hand, severe hypertension (blood pressure $\geq 180/100$ mmHg) was seen in both hypertensive and normotensive trekkers at each altitude (Table 3 and Figure 4). Occurrence of severe hypertension was similar across altitudes ($p<0.05$) and was predominately related to diastolic hypertension. It was observed more frequently at every altitude in trekkers with underlying hypertension. No subject was symptomatic.

The occurrence of severely elevated blood pressure varied between subjects taking different classes of antihypertensives (Table 4). Among hypertensive trekkers, ten took no medication and five of

those had one or more severe blood pressure measurements. Those five accounted for 21% of all severe blood pressures in hypertensive trekkers. Severely elevated blood pressure was observed most commonly in trekkers taking an angiotensin converting enzyme inhibitor or angiotension receptor blocker alone or in combination and accounted for another one-third of all those with severe hypertension. No subject taking a beta-blocker alone or in combination, or thiazide as monotherapy had severely elevated blood pressure. Due to small numbers of subjects taking each class of antihypertensive medication, statistical comparisons were not performed.

We enrolled 8 subjects for 24-h ABP monitoring, 4 normotensive (2 men, 2 women), and 4 hypertensive (4 men). Data was insufficient or incomplete for 2 of the HTN-ABPM subjects. We observed an increase in nocturnal systolic and diastolic blood pressure in hypertensive but not normotensive subjects (Table 5 and Fig 5). Maximum and minimum blood pressures (table 5), and number of blood pressures above normal (data not shown) were similar across all subjects. Severe hypertension was recorded in 3 normotensive subjects and in 2 hypertensive subjects. No subjects noted symptoms at the time of these BP readings.

Discussion

Altitude had minimal impact on blood pressure in our study. Mean systolic blood pressure did not change across altitudes and although mean diastolic blood pressure was statistically higher in normotensive trekkers at 3400m and 4300m, we do not consider the difference of 2 mmHg clinically relevant. As expected, mean blood pressures were higher in those with underlying hypertension. Contrary to our hypothesis, blood pressure was more likely to decrease at higher altitudes in hypertensive trekkers than in normotensive trekkers. However, individual blood pressure response to

altitude varied greatly in both groups. Severely elevated blood pressure was seen infrequently in participants with and without underlying hypertension, and there were no incidents of symptomatic hypertension.

Our large cohort enabled us to demonstrate that individual changes in blood pressure at consecutive altitudes occurred in a nearly normal distribution with few subjects having large changes in either direction. This inter-individual variability likely explains the mixed results seen in previous studies (Luks 2009), (Roach, Houston *et al.* 1995), (Bilo, Caldara *et al.* 2011), (Parati, Bilo *et al.* 2014) since these studies all reported mean values, which may be skewed by even one individual with a very high or very low value. Our large sample size allows us to conclude that in the majority of people, blood pressure will change minimally up to altitudes of 4300m, although a small proportion of trekkers may have a more drastic increase or decrease.

A prior study by Parati *et al* demonstrated that blood pressure increased in normotensive subjects at altitudes above 4300m, but individual responses were not reported (Parati, Bilo *et al.* 2014). Our results do not exclude the possibility that as hypoxic stress increases at altitudes above 4300m, blood pressure may be more likely to rise. However, for altitudes that most travelers encounter in the United States and Europe, our results suggest that few will have clinically important changes in their arterial pressures.

It has been suggested that blood pressure may change acutely on exposure to high altitude and then normalize over time due to acclimatization (Levine, Zuckerman *et al.* 1997). Roach *et al* demonstrated in 64 normotensive and 33 hypertensive older subjects that mean blood pressure was higher at 2500m than historical home measurements, and that it decreased until stabilizing on day three (Roach, Houston *et al.* 1995). This pattern was similar in subjects with and without hypertension, though like our subjects, those with hypertension tended to have higher pressures. The individual measurements

and exact mean blood pressure values are not provided in the study, but the graphs suggest most changes at altitude were within 10mmHg, similar to what we observed (Roach, Houston et al. 1995). On the contrary, Levine *et al* found a decrease in blood pressure on acute exposure to 2500m in a hypobaric chamber compared to arterial pressure at sea level and a normalization to near baseline after five days of acclimatization at 2500m in Vail, Colorado, but blood pressures from the first day in Vail were not reported (Levine, Zuckerman et al. 1997). Unlike the hypobaric chamber portion of this study, we could not measure hour-to-hour changes and the exact amount of time at 2860m varied between individuals, though all were within 24 hours of arrival to that altitude

In our study, blood pressure at 2860m was higher than reported home blood pressure in most individuals, but was still within the normal range in subjects without hypertension. It is debatable whether the increase at 2860m compared to self-reported home blood pressure reflects a real difference given the limitations of self-reported data (Parati, Stergiou et al. 2008). Of note, mean blood pressure did not change further on ascent to 3400m and 4300m in either normotensive or hypertensive subjects. We also observed no difference between ascending and descending measurements. These data support the idea that acclimatization serves to normalize blood pressure. We assert that in most people, altitude has little clinically important effect on blood pressure, regardless of acclimatization.

High altitude has been reported to cause dramatic increases in blood pressure in some patients (Bachman, Day et al. 2004) but the importance of asymptomatic short term arterial hypertension at high altitude is unclear. In asymptomatic patients at sea level, severe hypertension of short duration is not associated with adverse outcomes [8](Patel, Young et al. 2016). Furthermore, we could not identify any publications describing symptomatic patients or adverse outcomes due to extreme elevated blood pressure at high altitude. Though we observed severe hypertension in a small proportion of both normotensive and hypertensive subjects, none of them were symptomatic, similar to previous reports

(Roach, Houston *et al.* 1995, Wu, Ding *et al.* 2007). In addition, we observed that isolated severe diastolic hypertension was more common than systolic hypertension. This may be due in part to decreased stroke volume well described at high altitude.(Bärtsch and Gibbs 2007)

We cannot determine from our study whether the severe hypertension we observed was altitude-related or due to uncontrolled underlying hypertension. It is notable that, of the 20 patients with underlying hypertension who demonstrated extremely elevated blood pressure, half of them were not taking antihypertensive medication. They may have had uncontrolled hypertension at their sea level homes as well. In addition, in normotensive subjects, the subset that demonstrated very elevated pressures may have had undiagnosed hypertension. Given the lack of hypertension-related symptoms in our subjects, our results suggest that the best course of action for patients with well-controlled underlying hypertension traveling to high altitude is to continue their current medications without the need for routine blood pressure monitoring.

Which medications are best at controlling blood pressure at high altitude is unclear. Our preliminary results suggest that certain classes of antihypertensives may be more effective at high altitude than others. For example, no subject in our study taking a beta-blocker, alone or in combination, had an episode of severe hypertension. Increased catecholamines and sympathetic activation has been well documented at high altitude and beta-blockers as sympathetic antagonists blunt this response (Malhotra, Selvamurthy *et al.* 1976, Moore, Cymerman *et al.* 1986, Wolfel, Selland *et al.* 1994, Grover, Selland *et al.* 1998) and may explain this observation. Bilo *et al* showed that a combination of telmisartan and nifedipine, an ARB and a dihydropyridine calcium channel blocker, was effective in controlling blood pressure in hypertensive subjects at 3260m (Bilo, Villafuerte *et al.* 2015). Similarly, none of our subjects taking ACEIs or ARBs in combination with dihydropyridine calcium channel blockers developed severe hypertension. Our results also suggest that ACEIs or ARBs as monotherapies

may be least effective in preventing episodes of severe hypertension. Further study is warranted to address the question of which class or combination of antihypertensive medications is best at controlling blood pressure at high altitude.

Although limited by small number of participants, results from the subjects who underwent 24h-ABP monitoring suggest that subjects with hypertension may have a different nocturnal response to altitude than those without. However, we cannot say whether the absence of nocturnal so-called dipping in subjects with hypertension was altitude related or if they would have similar responses at sea-level, though this pattern is not seen in all patients with hypertension at sea level(2011). The clinical significance of this finding is also unclear, but may warrant further investigation.

Limitations

Our study has several important limitations. Individual health information was self-reported; recollection may or may not match medical records. Our study design prevented us from obtaining measured sea level home baseline blood pressures and self-reported numbers may not be accurate.

The loss to follow up of participants at 4300m was high and the sample size of hypertensives was smaller than the target of 36 at this altitude. We cannot confirm whether some of these subjects dropped out because of medical problems that may have influenced by or been due to blood pressure. Attrition was also sporadic, leading to incomplete data sets in some individuals.

Additionally, there is potential selection bias because our volunteer participants were mostly English speaking. We are unable to compare those who agreed to participate in our study to trekkers and guides who declined to participate, and we cannot say if they differed in any important ways. We sampled a relatively large proportion of all trekkers in the region during our study time period making it likely we have a representative sample(Keyes, Mather et al. 2016).

We studied trekkers with a relatively slow ascent profile who were walking daily. Our results may not apply to situations including acute exposure, rapid ascent, or in those not exercising at altitude. We did not routinely obtain more than one blood pressure reading and we cannot exclude that some elevated pressures were due to an alerting reaction however, it is not clear that this would be eliminated by additional readings as all but one of the volunteers measuring blood pressure were physicians (Mancia, Parati et al. 1987). We also did not quantify salt consumption or other dietary factors, though available food commodities and at trekking lodges is similar along the trekking route we studied which helps reduce variability. We also did not ask patients to void before measurements. Finally, we could not control for temperature variations at each altitude, though indoor temperatures were likely similar at 2860m and 4300m. Temperatures may have been colder at 3400m. Generally, this would serve to increase blood pressures (Saeki, Obayashi et al. 2014) at 3400m and accentuate any altitude-related effects, yet we saw no mean differences, and percent of subjects with increase in blood pressure was similar between each altitude.

Finally, we were able to perform 24-hour ambulatory measurements in a small subset of patients only. Isolated resting blood pressure measurements may be less accurate than continuous pressure monitoring. However, given the consistency within subjects across altitudes, and between ascending and descending measurements, our spot data are likely reasonable representatives of resting blood pressure.

Conclusions

In most individuals, both with and without hypertension, blood pressure is likely to change less than 10 mmHg at altitudes up to 4300m. Based on our results, travelers, including those with well controlled hypertension, can be reasonably reassured that their blood pressure will remain relatively stable at high altitude and they should continue their current medications. Though extremely elevated

blood pressure may be observed at high altitude in both normotensive and hypertensive people, it is unlikely to be associated with hypertensive emergencies. Further study is required to determine if there is an optimal antihypertensive regimen effective at high altitude.

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Transparency declaration: LK affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; and that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure Legends

Fig. 1 Flow of subjects through the study. Some subjects may have not had measurements at one altitude but then reappeared for measurements at subsequent altitudes.

Fig. 2 Distribution of blood pressure measurements among individuals at each altitude. Horizontal bars represent the number of trekkers per altitude with a systolic blood pressure measurement value as indicated on the y-axis.

Fig 3. Change in measured blood pressure between 2380m and 3400m and 3400m and 4300m in individual normotensive and hypertensive trekkers.

Fig 4. Extremes of blood pressure in normotensive and hypertensive trekkers at each altitude on ascent and descent.

Fig 5. Mean systolic blood pressure of each individual with 24-hour ambulatory blood pressure measurements.