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BRIEF REPORT

Ankle-Brachial Index on Kilimanjaro: Lessons from High Altitude

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Objective.—This study investigated the effects of a high–sympathetic stimulus environment (high-altitude hypoxia) on limb-specific systolic blood pressure (sBP) and ankle-brachial index (ABI) in normal volunteers. We hypothesized that currently accepted normal values for ABI may in fact not reflect an actual normal vascular state in all patients.

Methods.—Twenty climbers (17 males, 3 females) from Gatineau-Hull (Québec, Canada) participated in this study and ascended Mount Kilimanjaro, Africa. Ankle-brachial index measurements were performed at sea level and on Mount Kilimanjaro at ~4100 m. The data were analyzed using predictive analytics software SPSS 14.0. Data obtained at sea level were compared to those obtained at ~4100 m, with participants serving as their own controls.

Results.—Ankle-brachial indices measured at ~4100 m (mean = 1.20) were greater than those measured at sea level (mean = 0.97) ($n = -6.23$; 95% CI: −.32 to −.17; $P < .001$). There were no significant differences between the systolic brachial pressures at ~4100 m when compared to those at sea level ($P = .814$). Contrarily, systolic ankle pressures at sea level (mean = 132) were significantly greater than those measured at ~4100 m (mean = 152) ($t = -3.5$, 95% CI: −29 to −7.4; $P = .002$).

Conclusions.—This study is the first to physiologically demonstrate that in response to a high adrenergic stimulus in healthy volunteers there is a greater increase in sBP in the legs vs the arms.

Introduction

Peripheral arterial disease (PAD) is significantly more common in the lower extremities than it is the upper extremities.[1] Recent investigations have demonstrated that there is heterogeneous α1-adrenergic receptor responsiveness in human limbs, with legs responding to a greater extent than arms to adrenergic stimuli.[2] This important discovery opens the door to the notion of hypertension in the legs in the absence of detectable hypertension in the arms. In turn, as hypertension is one of the strongest independent risk factors for PAD,[3] this may explain why there is such predominance for occlusive disease in the lower extremities.

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The goal of this study was to investigate the effect on systolic blood pressure (sBP) and ankle-brachial index (ABI) of normal volunteers exposed to a high–sympathetic stimulus environment (high-altitude hypoxia). Twenty healthy individuals participated in an expedition to Mount Kilimanjaro in Africa. At an altitude of ~4100 m, acute acclimatization and exposure to hypoxia drive a strong sympathetic response.[4] We hypothesize that given the increased responsiveness to sympathetic stimuli in the legs, we would see an increase in sBP in the legs in the absence of a concomitant rise in the arms. We aimed to explore for the first time potential changes in ABI and sBP in the tibial artery in normal volunteers.

Material and Methods

SAMPLE

Twenty climbers from the Gatineau-Hull region in Québec (QC) ascended Mount Kilimanjaro (Africa) from November 25 through December 6, 2006. Consent to participate and release of baseline data for this study

Table 1. Demographic variables ($N = 19$)*

	Age	*Weight (kg)*	*Height (cm)*	*BMI (kg·m^{-2})*	*Waist (cm)*
Mean	42.5	79.0	1.7	25.6	91.6
Range	30.0–54.0	47.0–113.0	1.6–1.9	18.5–31.8	66.0–114.0
SD	6.9	15.6	0.1	3.5	12.7

*BMI indicates body mass index; Waist, circumference of waist.

were obtained prior to departure. Baseline fitness was assessed by Kinexsport (Gatineau, QC, Canada) prior to departure. Measured variables included the following: demographics (age, sex), previous level of physical activity, body mass index (BMI), Bruce test (predicted Vo_2 max), blood pressure and heart rate (resting, exercise), muscular strength and flexibility, overall score for 'back' health, and overall fitness score. All climbers were placed on acetazolamide (Diamox) 125 mg twice daily to prevent acute mountain sickness.[5] Baseline values were measured prior to volunteers beginning prophylactic acetazolamide.

All baseline ABI measurements were made by registered vascular technologists. All altitude ABIs were completed by a single examiner. The examiner is a certified vascular surgeon (CSSSG-Hull, QC, Canada) and registered vascular technologist (Canada), who is director of a laboratory accredited by the Intersocietal Commission for the Accreditation of Vascular Laboratories (ICAVL, CSSSG-Hull, QC, Canada). The examiner was blinded to all baseline clinical data.

Ankle-brachial indices were measured at 2 different points in time: 1) Baseline (sea level)—ICAVL (Gatineau, QC, Canada) and 2) ~4100 m in altitude—Mount Kilimanjaro (Africa). Climbers were assigned to 1 of the 3 altitude testing days (day 2, 3, or 5) using random number assignment. Given the short time the volunteers were at altitude prior to pressure measurements, it was felt that acclimatization would not affect values.

Ankle-brachial index measurements were obtained using a standardized method,[6] and the equipment was appropriately calibrated prior to assessment. Equipment included the following: sphygmomanometer (Welch-Allyn, Skaneateles Falls, NY) with standard adult blood pressure cuff, Doppler flowmeter (Hadebo Minidop ES-100VX, Koven Technology, Winnepeg, Manitoba, Canada), ultrasound gel (Aquasonic, Parker Laboratories, Mississauga, Ontario, Canada), and fingertip pulse oximeter (Nonin Onyx 9500, Plymouth, Minnesota). Each participant was given a 1-hour rest period in a tent prior to assessment. Measurements were obtained at 1700 hours on each occasion. Climbers were placed in a supine position for 5 minutes prior to measuring the ABI. The clothing was removed exclusively for measurement and immediately repositioned. Only one limb was exposed at a given time.

ANALYSIS

A database was created using predictive analytics software SPSS 14.0. All quantitative data were grouped according to the participant's identification number and subsequently analyzed. The ABI is calculated by dividing the systolic pressure of the ankle by the systolic brachial pressure. This value was calculated using both the anterior tibialis and dorsalis pedis pressures, and the highest value was kept for analysis, as per standard technique.[6] Descriptive analyses were computed for demographic and baseline health variables. Comparison analyses were performed, with a P-value set at .05. First, using a paired t test, for each individual as well as collectively, ABIs from ~4100 m were compared to those obtained at sea level.

Results

DEMOGRAPHIC AND CARDIOVASCULAR ANALYSIS

Twenty climbers (17 males, 3 females) participated in this study. None of the climbers experienced acute mountain sickness. Sample demographics and baseline cardiovascular results are presented in Tables 1 and 2, respectively. Overall fitness assessment (global score of baseline testing) revealed that 58% of climbers were rated as having ''excellent'' fitness, 22% ''very good'' fitness, 10% ''good'' fitness, 10% ''acceptable'' fitness, and none ''poor'' fitness.

ABIs: Sea level vs ~4100 m

As shown in Figure 1, ABIs measured at ~4100 m were found to be significantly different than those measured at sea level ($n = 20$; $t = -6.23$; 95% CI: -0.32 to -0.17; $P < .001$). In all cases, ABIs at ~4100 m (mean = 1.20, range = .96–1.45) were greater than those at sea level (mean = 0.97, range = .86–1.07).

Table 2. Baseline cardiovascular variables*

	Resting HR (bpm)	*Systolic BP at rest†*	*Diastolic BP at rest†*	*ABI (tibial)*
Mean	70	126	78	0.97
Range	57–88	99–156	62–92	0.86–1.07
SD	9	15	7	0.70

*N = 20, except for Resting HR, where N = 19; HR indicates heart rate; bpm, beats per minute; BP, blood pressure (mm Hg); †, brachial pressure; ABI, ankle-brachial index.

Systolic brachial and ankle pressures: Sea level vs ~4100 m

Although the mean brachial systolic pressure at ~4100 m (126.53) was greater than that at sea level (125.84), there was no significant difference (P = .814).

As shown in Figure 2, systolic ankle pressures at sea level (mean = 132.89) were significantly different from those measured at ~4100 m (mean = 151.84) (n = 20; t = −3.5; 95% CI: −29.3 to −7.4, P = .002). That is, the absolute systolic ankle pressure for all participants increased at high altitude when compared to their sea level measurements, with the exception of one climber, in whose case the systolic ankle pressure was unchanged. The increase in ABIs at ~4100 m when compared to sea level can therefore be accounted for by the significant increase is systolic ankle pressure.

Discussion

As hypothesized, this study reveals that normal volunteers exposed to a high–sympathetic stimulus environment (high-altitude hypoxia) exhibit a greater increase in sBP in the legs than in the arms. To our knowledge, this study is the first to demonstrate such data outside of the confines of a physiological laboratory study.

HYPOXIA AND HIGH ALTITUDE AS A "SYMPATHETIC STIMULUS"

Hypoxia is an important trigger of the sympathetic nervous system. Hypoxia increases the expression of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, and leads to increased α1-adrenoreceptor messenger RNA and, thus, receptor expression, by up to a fivefold measure in arterial smooth muscle cells.[7] It is well known that at high altitude adrenergics (epinephrine and norepinephrine), the major neurotransmitters of the sympathetic nervous system, interact with α-adrenergic receptors to regulate key physiologic processes, including vascular resistance and blood pressure. Blockade of the α-adrenergic system at altitudes of 4300 m has been proved to affect key adaptations associated

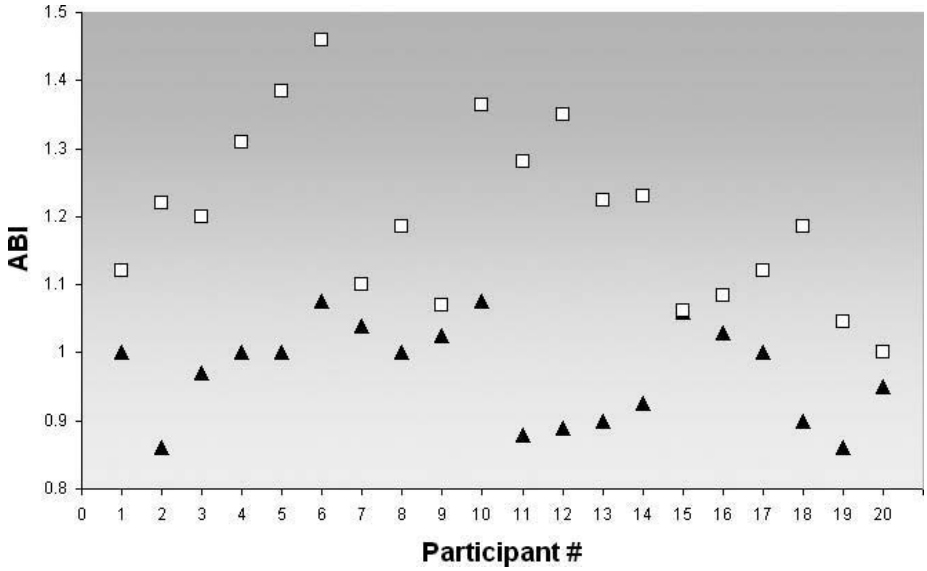

Figure 1. Comparison of ankle-brachial index (ABI) at sea level (baseline) and at ~4100 m (N = 20). Closed triangles (▲) represent sea level ABI and open squares (□) represent ABI at ~4100 m.

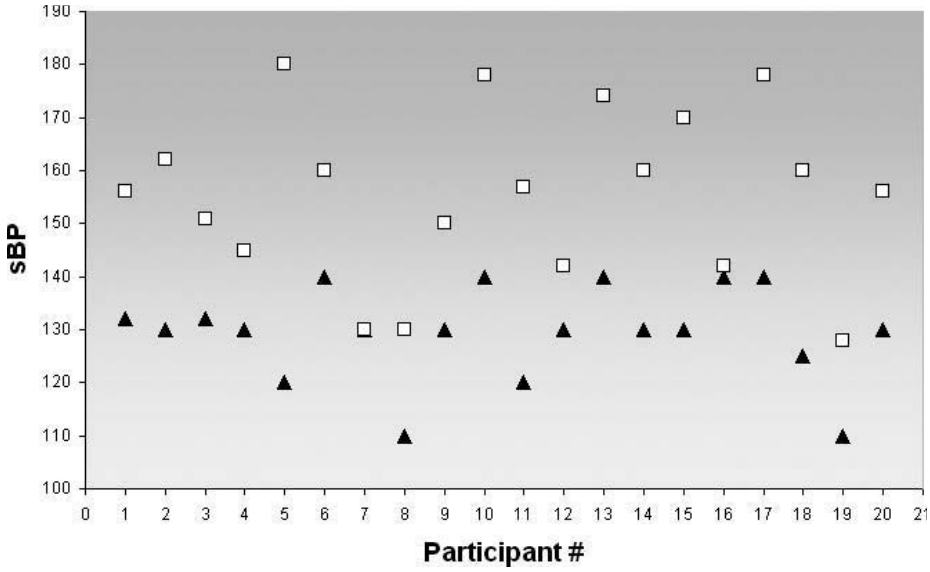

Figure 2. Comparison of systolic ankle pressure measurement at sea level (baseline) and at ~4100 m ($N = 20$). Closed triangles (▲) represent sea level measurement and open squares (□) represent measurement at ~4100 m.

with acclimatization: namely, volunteers receiving prazosin, a selective α1-adrenergic antagonist, exhibited a blunting of the expected rise in sBP at high altitudes.[8]

HETEROGENEOUS RESPONSES OF HUMAN LIMBS

Humans, unlike quadrupeds, are regularly exposed to significantly greater pressures in the legs compared to the arms. Much of our time is spent upright, and hydrostatic pressures in the legs contribute to a transient elevation in blood pressure. The arms, to the contrary, lie approximately at the level of the heart and therefore exhibit pressures that are closer to those of the aorta. It is known that responses to adrenergic stimuli are not the same in the arms and legs. Pawelczyk and Levine[2] have shown that there is heterogeneous α1-adrenergic receptor responsiveness in human limbs. Hypothesized molecular mechanisms to explain these findings include disproportionate α1-adrenergic receptor distribution in the lower extremities and variation in receptor sensitivity. Additionally, other investigations indicate that the legs have a greater sympatholytic capacity.[9] Although the cause is not yet clear, this study clearly demonstrates that, in healthy volunteers, sBP in lower extremities rises to a significantly greater extent than upper extremities in response to a sympathetic stimulus. This investigation leads us to wonder what should be the accepted 'normal upper limit' for the ABI.

This idea raises many prospects for future research. We know that tobacco smoking induces a state of relative tissue hypoxia, namely, through mechanisms of decreased blood oxygen carrying capacity and increased blood-O_2 affinity.[10] Given the outcome of the present study, it would be interesting to follow a cohort of smokers to determine whether this population is at increased risk of developing hypertension in the legs as a predecessor to systemic hypertension and/or PAD. We hypothesize that in the asymptomatic years prior to development of claudication, if we were to systemically measure blood pressures in the legs, we would find that it would be higher in smokers than in nonsmokers, similar to what the participants of this study experienced on Mount Kilimanjaro, where they were exposed to a hyperadrenergic state. It would be very interesting to determine if an ABI above 1.1 is, in fact, not normal and is the first sign of PAD.

Study limitations

The main limitation of this study is that only 1 measurement of ABI per climber was taken. However, given the narrow confidence intervals, one can safely assume that values did not exhibit significant discrepancies. Further, the cohort of volunteers is small, and larger group analysis may allow greater statistical significance. Baseline values were not performed with volunteers on acetazolamide, but to our knowledge, this drug does not affect systolic blood pressure and, therefore, it is valid to compare baseline and altitude values for these volunteers. Every precaution was taken to ensure normothermia in volunteers prior to measurements to avoid the

contribution of cold-induced vasoconstriction to the rise in blood pressure in the lower extremities. We did not specifically measure sympathetic activation as we felt there is sufficient literature to support the role of hypoxia as a sympathetic trigger. Finally, these findings were gathered in high-altitude hypoxic conditions for the first time, and it is unknown if other factors unique to high altitude may be contributing to these results and whether or not they will be reproducible at sea level in the face of similar sympathetic stressors, such as acute hypoxic gas breathing.

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