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Cardiovascular function in healthy Himalayan high-altitude dwellers

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ABSTRACT

Background: Residents of the Himalayan valleys uniquely adapted to their hypoxic environment in terms of pulmonary vasculature, but their systemic vascular function is still largely unexplored. The aim of the study was to investigate vascular function and structure in rural Sherpa population, permanently living at high altitude in Nepal (HA), in comparison with control Caucasian subjects (C) living at sea level.
Methods and results: 95 HA and 64 C were enrolled. Cardiac ultrasound, flow-mediated dilation (FMD) of the brachial artery, carotid geometry and stiffness, and aortic pulse wave velocity (PWV) were performed. The same protocol was repeated in 11 HA with reduced FMD, after 1-h 100% O_2 administration.
HA presented lower FMD (5.18 ± 3.10 vs. 6.44 ± 2.91%, $p = 0.02$) and hyperemic velocity than C (0.61 ± 0.24 vs. 0.75 ± 0.28 m/s, $p = 0.008$), while systolic pulmonary pressure was higher (29.4 ± 5.5 vs. 23.6 ± 4.8 mmHg, $p < 0.0001$). In multiple regression analysis performed in HA, hyperemic velocity remained an independent predictor of FMD, after adjustment for baseline brachial artery diameter, room temperature and pulse pressure, explaining 8.7% of its variance. On the contrary, in C brachial artery diameter remained the only independent predictor of FMD, after adjustment for confounders. HA presented also lower carotid IMT than C (0.509 ± 0.121 vs. 0.576 ± 0.122 mm, $p < 0.0001$), higher diameter (6.98 ± 1.07 vs. 6.81 ± 0.85 mm, $p = 0.004$ adjusted for body surface area) and circumferential wall stress (67.6 ± 13.1 vs. 56.4 ± 16.0 kPa, $p < 0.0001$), while PWV was similar. O_2 administration did not modify vascular variables.
Conclusions: HA exhibit reduced NO-mediated dilation in the brachial artery, which is associated to reduced hyperemic response, indicating microcirculatory dysfunction. A peculiar carotid phenotype, characterized by reduced IMT and enlarged diameter, was also found.

1. Introduction

Many residents of the Himalayan valleys and Tibetan Plateau live at high altitude, experiencing O_2 concentrations that are about 40% lower than those at sea level. Compared to other populations living at high altitude, such as Andean populations, they developed a favorable phenotype, characterized by lower prevalence of pulmonary hypertension and polycythemia despite decreased arterial O_2 content [1–5]. In particular, O_2 delivery to the cells is suspected to be maintained by compensative modulation of pulmonary vascular flow, probably due to tonically elevated pulmonary NO production [6,7]. NO is a key molecule in systemic and pulmonary vascular physiology, for its vasodilating, antithrombotic and antimitotic properties [8]. Reduced NO availability in the systemic circulation, which is the main feature of endothelial dysfunction, has been recognized as the first step towards development of atherosclerosis [8]. Acute hypoxia can induce endothelial dysfunction and activation in individuals living at sea-level [9,10]. Furthermore, diseases characterized by chronic hypoxia show reduced NO-mediated vasodilation [11]. However, systemic vascular characteristics of populations chronically exposed to hypobaric hypoxia are still unknown. We hypothesized that chronic exposure to hypobaric hypoxia might impair systemic endothelial function, thus favoring the development of cardiovascular damage.

Accordingly, the aim of the study was to investigate the presence of reduced NO-mediated vasodilation in rural Sherpa population,

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permanently living in Khumbu Valley (Nepal) at high altitude. In order to assess the presence of subclinical cardiovascular damage and its association with endothelial dysfunction, we measured a panel of established biomarkers (aortic and carotid stiffness, carotid intima-media thickness, left ventricular mass and diastolic function). Furthermore, pulmonary pressures were estimated, to evaluate response to hypoxia in the pulmonary vasculature.

2. Methods

2.1. Study population

The study was part of the SHARE project (Stations at High Altitude for Research on the Environment). The study population was constituted by 95 high-altitude dwellers (HA), born and permanently living in the Khumbu Valley (Nepal), enrolled by local advertising in three rural villages (altitude 2600, 3800 and 3800 m respectively). Criteria of inclusion were age between 15 and 65 years, apparent good health status, and written informed consent. Criteria of exclusion were known established cardiovascular or renal disease, cardiovascular risk factors or treatments, active infections or neoplasm, pregnancy. We compared the vascular features of HA with those of 64 Caucasian subjects (C), living and studied at the sea-level in Italy, recruited according to the same criteria, and matched for age, sex, mean blood pressure (BP), and body mass index (BMI). All the subjects enrolled were aware of the purposes of the study and gave written informed consent. The study was conducted with the approval of the Ethical Committee in Italy and of the Nepal Health Research Council (NHRC) (Kathmandu, Nepal) and of the Nepal Academy of Science and Technology (NAST) (Clinical Trials Gov Registration #NCT01329159).

An extended version of the Methods section is available as Online-only Supplement.

2.2. Experimental protocol

All measurements were performed in the morning after an overnight fasting, in a quiet room. Medical history was collected by Nepalese-speaking physicians (R.S. and G.B.T.). Brachial BP was measured with the individual resting in a supine position for at least 10 min, three times at 2-min intervals, and averaged on the last two measurements. Finger O_2 saturation (SO_2), weight and height were also taken.

2.3. Echocardiography

Left ventricular (LV) dimensions were taken and used to calculated LV mass [12]. LV ejection fraction (EF) was calculated by the modified biplane Simpson's method [12], while cardiac output was calculated from LV outflow tract diameter and time-velocity integral [13]. Doppler mitral E flow-velocity wave and tissue Doppler mitral annulus flow e′ early diastolic velocity were acquired for the calculation of E/e′. Systolic pulmonary artery pressure (PAP) was estimated from a trans-tricuspid gradient (right atrium − right ventricle gradient, RA-RV gradient) calculated from the maximal velocity of continuous Doppler tricuspid regurgitation [13,14]. Mean PAP, left atrial pressure (LAP) [15] and pulmonary vascular resistance (PVR) were also calculated [16].

2.4. Vascular function and structure

Endothelium-dependent response was assessed by ultrasound as increase of the brachial artery diameter (BAD) in response to increased blood flow (flow-mediated dilation, FMD), as previously described [17,18]. Endothelium-independent dilation was obtained by sublingual administration of 25 μg glyceryl-trinitrate (GTN). Flow velocity (FV) was recorded throughout the recording, and baseline and hyperemic FV were computed.

Carotid geometry and stiffness variables were assessed by the automated analysis of common carotid ultrasound scans [19]. Carotid distension (ΔD), cross-sectional distensibility coefficient (DC) and compliance coefficient (CC) were calculated. Common carotid intima-media thickness (IMT) was automatically measured on the same image sequences, and wall to lumen ratio (W/L) and static circumferential wall stress were computed [20].

Carotid-femoral and carotid-radial pulse wave velocity (PWV) were assessed by applanation tonometry (PulsePen, Diatecne: Milan, Italy), according to international recommendations, as previously described [17]. Carotid systolic BP and pulse pressure (PP) were then obtained from carotid pressure waveform, using brachial BP for calibration, as well as carotid augmented pressure and augmentation index [21].

2.5. Effect of O_2 administration

In order to assess the role of hypoxia per se in inducing endothelial dysfunction, in 11 subjects with reduced FMD (below the median value in the HA population), the protocol was repeated after 100% O_2 administration for 1 h, titrated to maintain SO_2 around 100%.

2.6. Statistical analysis

Statistical analysis was performed using NCSS 2008 (NCSS: Kaysville, Utah, USA). Results were expressed as mean ± SD. Differences in means among groups were analyzed using ANOVA for normally distributed variables, or Kruskal–Wallis Z Test for not normally distributed variables. Analysis of covariance was also used to compare vascular parameters, when indicated. An ANCOVA-based allometric approach was used in order to adjust for the influence of baseline diameter on FMD [22]. Categorical variables were analyzed by χ^2 test. Spearman's rank was used to explore correlations among variables. Multiple linear regression analysis was performed including parameters correlated with the dependent variable (FMD) with $p < 0.10$.

3. Results

3.1. Clinical and echocardiographic characteristics of the study population

As expected, HA had higher heart rate and lower SO_2 and body surface area (BSA) than C, but similar BMI. They also showed higher diastolic and lower systolic BP values, leading to a lower PP, in the presence of similar mean BP values, HA. Room temperature during the experimental sessions was significantly lower in HA than in C (Table 1).

LV systolic diameters and wall thickness corrected for body surface area, were not significantly different in HA and C, resulting in a similar LV mass index. LV diastolic diameter was significantly reduced in HA, but significance was lost upon adjustment for BSA and heart rate ($p = 0.10$). EF and cardiac output and E/e′ were comparable in the two groups under investigation. Systolic and mean PAP were significantly higher in HA than in C (Table 1), with 15 (15.8%) and 7 (7.4%) individuals presenting pulmonary hypertension, defined with a cut-off of 35 and 25 mmHg respectively. Also PVR were increased in HA as compared with C, with 19 (20.0%) individuals with PVR≥3 mmHg/min/L.