Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Original Article

Endothelial markers in high altitude induced systemic hypertension (HASH) at moderate high altitude

Lt Col Uday Yanamandra [a], *Lt Col S.P. Singh* [b], *Sushma Yanamandra* [c], *Lt Col Deepak Mulajkar* [d], *Maj Gen R.S. Grewal, VSM* [e], *Shashibala Singh* [f], *M.Z. Ashraf* [g,1], *Prasanna Reddy* [h], *Lt Gen Velu Nair, PVSM, AVSM, VSM**, (Retd)* [i,2,*]

[a] *Classified Specialist (Med) & Hematologist, Army Hospital (Research & Referral), Delhi Cantt 110010, India*
[b] *Associate Professor, Department of Physiology, Armed Forces Medical College, Pune, 411040, India*
[c] *Medical Officer, Max Hospital, Mohali, Punjab 160012, India*
[d] *Classified Specialist (Med) & Oncologist, Command Hospital (Southern Command), Pune, 411040, India*
[e] *MG (Med) Eastern Command Fort William, Kolkata, India*
[f] *DS & Director General, Life Sciences (LS), DRDO, Ministry of Defence, DRDO Bhavan, New Delhi 110011, India*
[g] *Former Scientist E &, Division Head, Genomics Division, DIPAS, DRDO, Timarpur, Delhi 110054, India*
[h] *Scientist F, DIPAS, DRDO, Timarpur, Delhi 110054, India*
[i] *Former Director General Medical Services (Army), Integrated Headquarters, Ministry of Defence, New Delhi 110001, India*

ARTICLE INFO

Article history:
Received 6 June 2017
Accepted 22 September 2017
Available online 15 November 2017

Keywords:
High altitude
Systemic hypertension
Endothelial dysfunction

ABSTRACT

Background: Chronic intermittent hypoxia is known to induce systemic arterial hypertension whereas chronic hypoxia causes pulmonary arterial hypertension. High altitude (HA) induced systemic hypertension (HASH) in previously normotensive lowlanders following acclimatisation and prolonged stay at moderate HA is a commonly encountered medical problem. HASH has been attributed to increased sympathetic discharge. Endothelial dysfunction (ED) is implicated in hypertension in the plains hence this study was conducted in HA. This is relevant especially because of the established role of ED in the aetiopathogenesis of HA illnesses. Since hypoxia may induce ED, we aimed at studying the association of endothelial dysfunction with HASH in temporary residents at HA.

Methods: In this case–control single-centre study, we evaluated ED, by measuring endothelial molecular markers, soluble intercellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (VCAM-1), vascular endothelial growth factor (VEGF) and endothelial selectin (E-Selectin) in 24 cases with HASH and 25 age, sex matched normotensive controls at moderate high altitude (11,500 ft).

* *Corresponding author.*
E-mail address: nairvelu2000@yahoo.com (V. Nair).
[1] Present address Professor, Department of Biotechnology, Jamia Millia Islamia, New Delhi 110025, India.
[2] Present address 632, C-1, Ansals Palam Vihar, Carterpuri, Gurgaon 122017, Haryana, India.

http://dx.doi.org/10.1016/j.mjafi.2017.09.010

Results: The levels of sICAM-1 (patients: 214.3 ± 34.2 μg/L, controls: 196.2 ± 28.5 μg/L; $p = 0.049$) and VCAM-1 (patients 766.1 ± 123.4 ng/mL, controls: 668.6 + 117.6 ng/mL; $p = 0.007$) were statistically higher in the patient group. However, VEGF and E-Selectin were not significantly different between the groups. sICAM-1 significantly correlated with levels of systolic and diastolic blood pressure ($r = 0.401$, $p = 0.003$ and 0.486, $p = 0.000$) respectively. *Conclusion:* HASH is associated with endothelial dysfunction in form of raised levels of sICAM-1 and VCAM-1.

Introduction

Chronic intermittent hypoxia (CIH), as in obstructive sleep apnoea (OSA), is known to cause systemic arterial hypertension (HTN), whereas, continuous hypoxia in healthy humans, as at high altitude (HA), is known to mediate pulmonary arterial hypertension.[1–3] Amongst lowland sojourners at HA, systemic blood pressure (BP) was found to be elevated both in the un-acclimatised and the well acclimatised state.[4] This increase during the initial exposure to HA is a part of the acclimatisation process to ensure sufficient tissue oxygenation in hypobaric hypoxia and subsides with in the first week of arrival to normal levels.[4] The submaximal and maximal exercise was found to further elevate the systemic BP at HA.[5] This elevation of BP has been shown to be due to increased sympathetic drive and could be attenuated but not abolished by the α-adrenergic blockade. The increase in sympathetic activity is known to be mediated by hypoxic chemoreflex mechanisms.[6]

Endothelial dysfunction (ED) can be determined by evaluation of endothelial markers, flow mediated dilation intimal media thickness and lately by intra-arterial ultrasonography.[7,8] Cellular adhesion molecules (CAM) play a major role in causation of atherosclerosis mediated by Selectins (causes rolling of leukocytes on endothelium) and vascular cell adhesion molecule-1 (VCAM-1)/soluble intercellular adhesion molecule-1 (sICAM-1) (causes binding of circulating leukocytes to vascular endothelium, and aids in leucocyte migration to sub-endothelial spaces).[9] Its levels increase in various conditions leading to atherosclerosis such as dyslipidaemia, diabetes mellitus, and chronic inflammatory states. The role of VCAM-1, endothelial-leucocyte adhesion molecule-1 (E-selectin) and sICAM-1 in the biology of atherosclerosis are well characterised.[10–13] On immunohistochemical studies, these molecules have been expressed variably but consistently within the atherosclerotic plaque.[14,15] Serum levels of these CAM have been elevated during inflammatory conditions with increased expression on endothelial cells and other tissue types, though their origin is still unclear and proposed to be secondary to shedding or proteolytic cleavage from endothelial cells.[16]

Endothelial dysfunction has been implicated in various HA illness (HAI) including high altitude pulmonary oedema (HAPE) and chronic mountain sickness (CMS).[17,18] However causal relation in high altitude systemic hypertension (HASH) is yet to be established. ED as a common contributor to hypoxia associated ailments at HA (such as HAI, HASH, CMS) is an attractive and plausible hypothesis. The findings of normalisation of urinary catecholamines by 90 days of stay at HA, the inability of a α-adrenoceptor blocker to obviate HTN on ascent/sojourn in chronic hypoxia and the likely involvement of angiotensin converting enzyme (ACE) in HASH – all suggest mechanisms in addition to sympathetic stimulation in the causation and/or sustenance of HASH.

It is suggested that the level of these endothelial markers increase on induction to HA owing to hypoxic stress. So, we hypothesise that the rise in these endothelial markers leads to increased systemic hypertension which was never studied in the past. Hence, we propose to measure various markers of ED (sICAM-1, VCAM-1, vascular endothelial growth factor (VEGF) and E-Selectin) in a patient with HASH. The aim was to study the level of ED markers (sICAM-1, VCAM-1, VEGF, and E-Selectin) and its association with HASH.

Material and methods

Study and control groups

This is a case–control single-centre study. All cases and controls were lowlanders sojourning at HA. The study was conducted in the Medicine department at a secondary care centre located at HA (11,500 feet) during the study period of 5 months (Aug 2012 – Dec 2012). All consecutive patients who underwent consultation for HASH meeting the inclusion criteria were included in the study (i.e., freshly diagnosed hypertension by joint national committee (JNC) VII criteria, age less than 40 years, not of Ladakhi/Tibetan ethnicity, and not Hypertensive before induction to HA). Exclusion criteria included (a) patients with less than 30 days duration of stay (from arrival at HA to symptom onset or detection of systemic HTN) (b) presence of any inflammatory states such as occurrence of acute HAI (HAPE, AMS and HACE on initial or re-ascent in the last 6 months), febrile illness and organ dysfunction.

An equal numbered age, sex, and ethnicity matched healthy controls with similar duration/altitude of stay at HA formed the control population. Study patients and controls were studied for their baseline epidemiological/laboratory parameters. The study protocol was approved by the institutional