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High Altitude Systemic Hypertension (HASH) - A New Entity

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INTRODUCTION

There are over 140 million people living worldwide at High Altitude (HA) of which 13 million are in Ethiopia, 1.7 million in Tibet (total 78 million in Asia), 35 million in the South America (Andes), and 0.3 million in Colorado Rocky Mountains. HA is defined in medical terms as an elevation of 2700 m above sea level. The numbers of people who reside or visit HA continue to rise. Troops of the Indian Army are stationed in the highest battlefield at Siachen glacier with altitudes varying from 15,000 to 23,000ft. HA tourism continues to be on the rise in India. The stays at these altitudes are fraught with multiple health/ medical issues known as High Altitude illnesses (HAI) such as high altitude pulmonary edema, high altitude cerebral edema, acute mountain sickness and chronic mountain sickness. The least described and minimally studied among these HAIs is the commonly occurring high altitude associated systemic hypertension (HASH).

CONCEPT BEHIND HASH: WHY SHOULD WE DEFINE A NEW ENTITY

Chronic intermittent hypoxia, as in obstructive sleep apnea, is known to cause systemic arterial hypertension (HTN), whereas, continuous hypoxia in healthy humans, as at HA, is known to mediate pulmonary arterial hypertension. In early reports of lowland sojourners at HA, systemic blood pressure (BP) was found to be elevated both in the un-acclimatized and the well acclimatized state. Submaximal and maximal exercise was found to further elevate the systemic BP at HA. There is a strong correlation between altitude and prevalence of systemic hypertension. The prevalence of systemic hypertension at HA has been reported from 37 - 62.4% in different series from Himalayas. Also, a study from India has demonstrated a higher prevalence of systemic hypertension in migrants as compared to natives born in Leh, Ladakh. Systemic hypertension occurring at HA is a type of secondary hypertension and might lead to increased long term morbidity and mortality. It is thus very important to define this highly prevalent entity for identifying these patients early and promptly managing them.

CARDIOVASCULAR CHANGES IN HA

HASH is a consequence of complex interplay of the cardiovascular changes in response to HA can be different in acute and chronic exposure. A brief summary of these changes are enumerated in Table 1.

HASH AND ITS INCIDENCE

HASH is defined as presence of sustained hypertension (>150/90mm Hg; as per JNC criteria) in lowlanders at HA (>2700m). HASH is a type of secondary hypertension wherein stay at HA acts as the predisposing factor. There is paucity of data on HASH as lowlanders staying for prolonged periods in HA (2-3y) in great numbers outside the military/ occupational reasons is unusual. There is no literature available as on date to explain what happens to these individuals with HASH who continue to stay in HA with/ without treatment. In our experience, 4% of all subjects inducted to HA in a sample population and 34% of admissions to Medicine department in a secondary care center situated at HA were due to HASH in a two year period of 2012-13. Data from HA medical research center (HAMRC, India) by Singh SP et al revealed that seven percent of hospital admissions of lowland sojourners at 3300m from 2001-2008 were due to hypertension. In another study, the same group found 30.6 % of 316 subjects at 3300m to be hypertensive on screening by JNC VII criteria that were normotensive in plains.

PATHOPHYSIOLOGY OF HASH

Many theories have been proposed, pathophysiology being multifactorial with sympathetic activation, hormonal imbalance (Table 2) and endothelial activation playing crucial role.

Role of Sympathetic Activation

The role of the autonomic nervous system in controlling heart rate (HR) and cardiac output is well established. Short periods of exposure to hypoxia increase the concentration of epinephrine and nor epinephrine, which leads to hypoxia induced increase in HR and BP. These alterations in the autonomic nervous system might play some role in alteration of blood pressure at HA. In a study of 9 healthy Danish lowlanders after 9 weeks at 5260m, Calbet et al showed a 3.8 fold greater whole body nor-adrenaline (NA) release compared to sea-level values. Both the systolic and diastolic blood pressure (SBP, DBP) values were significantly higher than sea-level. Whether a sustained increase in whole body NA release occurs in sojourners at HA as demonstrated at extreme altitude is not known, although, Sharma et al had reported a return of urinary catecholamines to sea-level values by 90 days stay in sojourners at 3300m. In a study of lowland Han subjects working on the Lhasa railroad project Wu et al found 45 subjects who were normotensive at sea-level but developed HTN between 3486-4509m. While the BP settled by day 12-21 in 33 subjects, in the remaining subjects it

Table 1: Cardiovascular changes in HA

	Acute Exposure	Sustained Exposure
HR (HR)	Elevation of HR in response to hypoxic challenge is attributed to the sympathetic stimulation and vagal withdrawal; however, intrinsic HR does not seem to be affected during acute exposure.	Resting HR seems to remain high despite acclimatization and does not reach sea level rates. Further increase in HR is seen with each increment in altitude. The decrease in plasma volume during the first few weeks in HA may unload the cardiopulmonary and arterial baroreceptors providing the continued stimulus to the sympathetic activation and at the same time causing vagal blockades leading to tachycardia.
Stroke volume:	Under acute conditions there seem to be no effects on the stroke volume. Classic studies at 4200m have documented up to 40% increase in cardiac outflow within days of ascent to HA. The magnitude of increase appears proportional to the hypoxia with no apparent increases below 700m of ascent.	Stroke volume is decreased and the reasons are manifold including decreased plasma volume, increased HR and more significantly diminished RV function consequent to increased pulmonary artery pressures. LV systolic function is rather unaffected at HA. The hypoxia tolerance of myocardium is attributed to heightened sympathetic drive, change of fuel to glucose/ lactate and transcriptional changes in mitochondrial nuclear genes. Consistent LV diastolic dysfunction has been noted with decreased distension; however, the volume depletion most probably masks the clinical manifestation of diastolic dysfunction.
Peripheral vascular resistance:	While the increase sympathetic drive on exposure to HA should have caused peripheral vasoconstriction, the hypoxia seems to override this phenomenon resulting in peripheral vasodilatation. This over-riding of the sympathetic stimulation by the local factors has been termed as functional sympatholysis.	The total sympathetic activity seems to increase with exposure to sustained hypoxia. The total peripheral resistance is the function of resistance in various regional vascular beds. The initial sympatholysis gradually decreases in response to improved CaO2 and subsequently the increased sympathetic drive seems to be the predominant factor.
Systemic blood pressure (BP):	The two diametrically opposite influences on the peripheral vascular resistance are increased adrenergic drive and functional sympatholysis, which determine the BP of the individual in HA. When BP is measured immediately on exposure to HA, there seems to be a slight hypotension. However over the next few hours there seems to be a modest increase in the BP due to reduction in plasma volume and subsequent increase in hemoglobin concentration. The regulation of the peripheral chemosensitive receptors by the total content of O_2 rather than the PaO_2 seems to be instrumental in this regard.	The BP measurements in lowlanders who are exposed to HA follow a pattern in which there is an immediate hypotension, followed by gradual rise in both diastolic and systolic BP as the functional sympatholysis response diminishes. However there is controversy over prolonged exposure (>90 days) to HA in that a few studies have reported return to sea level values, while others report sustained rise in BP.

Table 2: Hormonal changes on exposure to HA

	Acute Exposure	Sustained Exposure
Renin	Decreased	Decreased
Angiotensin II	No major shifts, may be decreased in few individuals	No major shifts in the levels
Aldosterone	Decreased	Decreased
Cortisol	No major change in hours	Increases secondary to hypoxic stress
Vasopressin	Decreased in initial hours	Increased over days to week and stabilizes in months

was significantly high even after 30-120 days. Descent to low altitude reduced the BP to pre-ascent values over 2-4 weeks but remarkably, eight of these subjects developed hypertension on each of four ascents leading to enforced descent and final removal from employment at HA. While their findings in the larger number of subjects are in consonance with the idea that sympathetic drive at HA settles with acclimatization the occurrence of repeated HTN in eight of their subjects on re-ascent to HA would suggest that a sub-set of healthy lowlanders are predisposed to sustained HTN with chronic systemic hypoxia at HA. Also study by Yanamandra et al revealed cardiac sympathetic-vagal imbalance in patients with HASH as evidenced by the abnormalities on heart rate variability (HRV) analysis.

Role of Endothelial Dysfunction

Endothelial dysfunction (ED) has been implicated in various HA illness (HAI) other than HASH previously. ED is also known to accentuate the risk of cardiovascular morbidity in various studies at sea level. ED can be determined by evaluation of endothelial markers, flow mediated dilation, intimal media thickness and lately by intra-arterial ultrasonography. In a study by the authors from India to elucidate role of endothelial dysfunction and HASH we found that the endothelial markers (sICAM and VCAM levels) were significantly higher in the patients with HASH when compared to the controls with similar duration of stay in HA. This rise could be either secondary to the inherent effect of the atherosclerosis in these individuals or the effect of the HA on unmasking the underlying ED. As we did not study the levels of cellular adhesion molecules (CAM) at sea level in these individuals so it is not possible to answer this question. Only conclusion which can be drawn from these results include that there is a significant difference in the above mentioned endothelial dysfunction markers between patients with HASH and controls. We also studied the flow mediated dilation in a group of patients with HASH in a case controlled fashion and found statistically significant differences.

Role of Conventional Risk Factors

Body fat content, is known to be associated with systemic hypertension at sea levels. A study conducted by the authors showed a significant relation between body mass index (BMI) and HASH. We also demonstrated a statistically significant correlation with obesity markers such as BMI, waist hip ratio (WHR) and actual body weight with HASH. The lipid profile revealed statistically higher cholesterol and LDL in patients with HASH against the controls but the values in either group were still in normal range. In another study by Singh SP et al from India revealed HASH subjects had a similar duration of stay, but had greater age, higher BMI and waist circumference than the control non-hypertensive population. 80.3% of the hypertensive patients were overweight/ obese by body fat criteria. Conventional risk factors for atherosclerosis would therefore appear to have a role in HASH. Another study from India by Kumar et al also found a greater BMI in eighteen subjects who developed HASH at 3300m compared to 28 who did not.

Role of Hormones In HASH

High altitude environment has a profound effect on most of the endocrine glands. Hypoxia is no doubt the major factor affecting endocrine function, but associated low temperatures and exercise are also factors affecting endocrine function. The hemodynamic and hormonal changes associated with HA exposure are illustrated in Table 2. Kumar et al from India, reported a significantly greater expression of the ACE D allele in subjects of HASH. This genetic expression was correlated to higher levels of ACE in these populations. In another study by us, patients of HASH displayed significantly greater levels of angiotensin II, norepinephrine, aldosterone/ARC and parathormone compared to normotensive subjects. All these factors are implicated to varying degrees in "essential" HTN in the plains too. It would therefore appear that at HA processes similar to those in the plains get accentuated in a sub-set of individuals resulting in development of HASH secondary to chronic hypoxia of HA. There was a definitive role of sympathovagal disturbance in the causation of HASH.

HOW TO DIAGNOSE?

The diagnosis is akin to the prevailing JNC guidelines in diagnosing hypertensive patients at sea levels, but for the necessity of continuous stay for more than 3 months at HA (>2700m) at the time of diagnosis in a lowlander. These definitions are arbitrary and primarily derived from studies conducted in HASH from India. Native highlanders with similar defining characters are not labelled HASH in the current studies as the data on the role of HA in such individuals is a topic of debate. There are studies to prove the benefit of ambulatory intermittent BP (AIBP) monitoring in diagnosing these patients earlier in HA. The lack of nocturnal dip in the BP is the earliest marker for these patients.

TREATMENT OF HASH

There are no guidelines on the management of the patients

Table 3: Take Home Message

- High altitude systemic hypertension (HASH) is a type of secondary hypertension following sustained exposure to high altitude.
- Sympathetic activation, endothelial dysfunction and hormonal imbalance in patients with conventional risk factors can predispose to HASH.
- Criteria for diagnosis are evolving and currently based on the criteria as defined in various clinical studies.
- De-induction to lower altitude/ sea levels can reverse the pathology with recurrence on re-induction to HA. ACE inhibitors and calcium channel blockers are preferred agents in studies with no proven literature on the ideal agent.

with HASH, it being a naïve field. There is no literature available as on date to explain what happens to these individuals with HASH who continue to stay in HA with/ without treatment. Investigators have variably used beta blockers, ACE inhibitors and calcium channel blockers either in isolation or in combination. We suggest the use of ACE inhibitors followed by calcium channel blockers for the effective control of these patients. In our settings, patients are de-inducted to lower altitude on diagnosis of HASH. Most of these patients become normotensive after 3-4 months of descent. On re-ascent these individuals develop recurrent HASH, with time to onset being earlier than the previous episode.

CONCLUSION

The diagnosis of HASH is fraught with controversies and the scientific community is divided on the mere presence of such an entity. Many argue it to be an extended part of the physiological continuum of the acclimatization process to hypobaric hypoxia. The thin line dividing the raised BP due to physiological acclimatization and the pathological process causing morbidities secondary to sustained hypertension needs to be defined. A tremendous contribution from the research community is required in clearly defining these different aspects of HASH. (Take home messages have been tabulated as Table 3)

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