Journal of
Proteomics & Bioinformatics

Paul et al., J Proteomics Bioinform 2015, 8:6
DOI: 10.4172/jpb.1000359

Research Article Open Access

High Altitude Pulmonary Edema: An Update on Omics Data and Redefining Susceptibility

Subhojit Paul[#], Anamika Gangwar[#], Aditya Arya, Kalpana Bhargava and Yasmin Ahmad*

Peptide and Proteomics Division, Defence Institute of Physiology and Allied Sciences, Defence Research and Development Organization, Lucknow Road, Timarpur, Delhi -110054, India
[#]Both the authors contributed equally to this work

Abstract

High altitude pulmonary edema (HAPE) is a serious pathological condition associated with rapid ascent to high altitude occurring in non-acclimatized but otherwise healthy individuals. Decades of scientific studies on HAPE have unraveled the disease pathology, diagnosis and therapeutic interventions yet, the etiology is still unknown. A vast scientific literature is available on HAPE for a quick reference of clinicians, researchers and academicians. Perhaps, the view of mountain travelers is different and their anticipation of HAPE susceptibility comprises of personal experience. Ever-increasing number of visitors to high altitude demands the possibility of HAPE susceptibility screening, however, scientific community is yet to find a staunch solution. This review is an update of recent information on HAPE susceptibility indicators from genomics, proteomics and metabolomics as well as information pertaining to treatment/prognosis of HAPE.

Keywords: High altitude pulmonary edema; Biomarker; Proteomics; Susceptibility

Introduction

High altitude is home for nearly 140 million people across the globe, and a significant number of people travel to high altitudes for recreational purposes like skiing, mountaineering; amplifying sporting prowess through high altitude training; pilgrimages and on duty. Mountains have always been admired as one of the most beautiful creations of nature. The environmental condition at high altitude i.e hypobaric hypoxia results in arterial hypoxemia due to reduced barometric pressure and unchanged fractions of inspired oxygen (FiO_2 20%) resulting in, challenges to the human physique and psyche, especially when, people from low altitudes ascent to an altitude beyond 2500 m at a rapid rate, culminating in several ailments and in worst scenario, death.

Although, no distinct geological boundary exists between high and low altitude from the medical perspective, but evidences on altitude related sickness, high altitude is generally considered as an elevation of 1500 m or above mean sea level is generally considered as high altitude. Further, it has been classified in three strata: high altitude, 1500-3500 m, very high altitude 3500-5500 m and extreme altitude >5500 m [1]. Rapid ascent to the altitudes above 2500 m is associated with several diseases like acute mountain sickness (AMS), high altitude cerebral edema (HACE), Monge disease (Chronic mountain sickness) and high altitude pulmonary edema (HAPE) [2]. Although initial phases of many of these diseases are reversible and have successfully been cured, prolonged persistence can prove lethal. HAPE is one of the most common diseases both in terms of prevalence and also in terms of scientific studies [3].

Evidences suggest that high altitude pulmonary edema (HAPE) is the leakage of protein-rich exudates from pulmonary vasculature into the alveolar airspace due to the combination of increased cardiac output and exaggerated pulmonary artery pressure (causing non-uniform vasoconstriction in pulmonary bed with subsequent over perfusion) as a result of hypobaric hypoxia and hypoxemia, serving as the two pronged weapon of high altitude so as to cause severe acute respiratory distress in the affected individuals [3-6]. HAPE develops upon rapid ascent to altitudes of above 2500, within 2-4 days of arrival, its hallmark victims being non-acclimatized but otherwise healthy individuals [3,4]. Its incidences are estimated in the range of 0.1-4.0% [5].

HAPE is a potentially fatal malady at high altitude and requires immediate medical attention accompanied ideally by a descent to lower altitude. HAPE was first introduced to medical literature in the 1930s by Alberto Hurtado in Peruvian Andes. By 1960s, Herb Hultgren and then Houston showed what was considered till then, pneumonia or congestive heart failure due to cold and exertion to be a non-cardiogenic form of pulmonary edema [3,6]. It had also been reported in high altitude dwellers who return from a low altitude sojourn to their native lands [4].

Over the past five decades, HAPE has been unraveled to a large extent in terms of pathophysiology, prevention and treatment. First by clinical observations then physiological observations leading to cellular, biochemical, molecular genetics and proteomics based investigations and insights. A few unanswered but very interesting questions however, remain.

This review is aimed at finding common ground among all the seemingly divergent and vast amount of research information that one finds regarding HAPE and presenting it in a cohesive, continuous, simplistic and compact manner. Although several classical and excellent reviews on HAPE have been published, the focus of this review is mainly on the information obtained from omics studies (Genomics, Proteomics and Metabolomics), and current scientific

***Corresponding author:** Yasmin Ahmad, Peptide and Proteomics, Defence Institute of Physiology & Allied Science (DIPAS), Defence Research & Development Organization (DRDO), Ministry of Defence, Delhi, India, Tel: 011-23883002; E-mail: yasminchem@gmail.com

Received April 21, 2015; **Accepted** May 28, 2015; **Published** June 03, 2015

Citation: Paul S, Gangwar A, Arya A, Bhargava K, Ahmad Y (2015) High Altitude Pulmonary Edema: An Update on Omics Data and Redefining Susceptibility. J Proteomics Bioinform 8: 116-125. doi:10.4172/jpb.1000359

view on diagnosis, prophylaxis and susceptibility of HAPE in light of this data. We have, however included some of the basic information on HAPE for better comprehension. This review is divided into three sections: first describing the basic pathophysiology of HAPE, second focusing on prospective biomarkers (genes, proteins or metabolites) based on the information from omics data, especially for explaining the susceptibility and third section describing current approaches for prophylaxis, diagnosis and therapy. Finally, future guidelines for prospective studies are summarized in concluding remarks.

Pathophysiology of HAPE

Understanding the pathophysiology is crucial for diagnosis and prognosis of any diseases, HAPE is a multifactorial pathophysiological condition and does not show one distinct feature. Patient history is therefore a key component in diagnosis as HAPE is always preceded by rapid high altitude ascent [2]. Nevertheless, other symptoms need to be clinically correlated. Several criteria and scoring systems have been developed to categorize the severity of disease and are in use for several decades amongst which Lake Louise criteria is being most widely used. Following text summarizes the impact of altered physiology on progression of HAPE and characteristic symptoms.

Physiological progression towards HAPE

High mean pulmonary artery pressure (>35-40 mmHg) sets off a chain reaction ending finally in HAPE and the resulting respiratory distress [4-6]. The increased yet uneven pulmonary artery systolic pressure (PAP) causes a mismatch of the ventilation-perfusion ratio in some areas of the pulmonary capillary beds, favoring over perfusion in areas with relatively less vasoconstriction. The endothelia of capillaries in these areas are debilitated by stress failure and become highly permeable. These areas then witness a surge in the accumulation of protein-rich extravascular fluid leading to patchy fluid filled alveoli in the lungs [3,5,6]. An interesting conclusion was made recently by Bouzat et al. [7] that the transient interstitial pulmonary edema observed in several climbers in the first 2 days after ascent to 4350 m is rather a blessing in disguise as it is a process related to acclimatization to high-altitude. This interesting idea thoroughly justifies the study by Cremona et al. [8] but partially contradicts their conclusion that it is a sign of subclinical HAPE. It has also been reported that pressures of 20 mmHg in pulmonary microvasculature is enough to cause early interstitial edema [3]. Only exaggerated pulmonary hypertension on its own will not always cause HAPE [9,10]. Both these observations lead us to the next mechanism that is crucial to HAPE progression, i.e. the imbalance between the amount of alveolar fluid secreted and its subsequent reabsorption [3,6,9]. This mechanism will be detailed in the following sections. Another interesting aspect of HAPE is the accompanying inflammatory response as a consequence of fluid that floods the alveolar airspaces a few hours after onset of disease [5,11].

Symptoms and risk factors

Lake Louise criteria determines an individual to be suffering from HAPE if (s)he presents any two of the following symptoms-chest tightness, cough, dyspnea at rest, marked decrease in exercise performance (excess fatigue) and two of the following signs-central cyanosis, pulmonary crackles, tachycardia (>110 beats/min) and tachypnea (>20 beats/min) [12].

From the clinical perspective, HAPE has been divided into three categories based on the severity of the above mentioned symptoms as summarized in Table 1.

The risk factors associated with development of HAPE are the rate of ascent (>350 m per day above 2000 m), the genetic and physiological constitution of the individual, race and family of the individual, the altitude traversed (especially sleeping altitude), any previous history of HAPE, exertion/exercise (particularly high-intensity exercise), cold, administration/intake of any sedatives, any recent infections or disease affecting the lower airways and an idiopathic tendency of pulmonary hypertension [9,13-19].

Susceptibility towards HAPE: Does Omics Data has an Answer?

Although a work of more than five decades on HAPE has significantly improved the understanding of pathophysiology, progression and diagnostic strategies, yet the biggest question about HAPE that still remains unanswered is, am I susceptible to HAPE? Cremona et al. [8] noted that 3 out of every 4 individuals among the mountaineers had mild subclinical HAPE within hours of a moderate ascent to 4559 m. He also concluded that if lung size was less than normal and rate of ascent and physical effort were great enough, most climbers developed HAPE, the risk not being completely attributable to genetic susceptibility. A recent review by Lou et al. [20] summarized key information on genomic data from high altitude acclimatization and diseases. High altitude and the resultant hypobaric hypoxia caused a number of maladaptive responses in the susceptible individual such as poor ventilatory response, increased sympathetic tone of pulmonary vasculature and inhomogeneous exaggerated pulmonary vasoconstriction accompanied by right ventricular overload. All these physiological changes caused an imminent rise in PAP. This rise in pulmonary artery pressure actually lies critical to progression of HAPE [4], but preceding HAPE are other physiological changes as well. These include reduced lung compliance, weakness of inspiratory muscles, reduced static lung volumes and impaired gas exchange [21]. Considering these evidences one may speculate the susceptibility as multifactorial variant that may be affected by age, sex, genetic makeup, diet, lifestyle and even prior exposure to high altitude [9,22,23].

Evidences from genomics

Previous studies showed that HAPE reoccurred in those with a clinical history, or belonged to specific races and families, were far more HAPE-susceptible. These, susceptible individuals had marked differences in characters like lung volume, lung density, lung mass, number of interlobular septa in lungs, PAP levels and nasal transepithelial potential differences at rest. These evidence indicated towards a genetic and cellular component in the etiology of HAPE [13,21,24-28]. A number of

Grade	Symptoms	Signs
1 – Mild	Dyspnea on exertion, dry cough fatigue while moving uphill	HR (rest) < 90-100 beats/min, RR (rest) <20 beats/min dusky nailbeds or exertional desaturation localized crackles,(if any)
2 - Moderate	Dyspnea at rest, weakness, fatigue on level walking, raspy cough	HR 90-110 beats/min, RR 16-30 beats/min, cyanotic nail beds, crackles present
3 - Severe	Dyspnea at rest, extreme weakness orthopnea, productive cough	HR > 110 beats/min, RR > 30 beats/min, facial & nailbed cyanosis; Bilateral crackles, blood-tinged sputum, stupor, coma.

Table 1: Stratification of altitude based on the pathophysiological changes obsevered during human ascent.

genomic studies had been performed using global genomics approaches such as microarray or using targeted approaches such as qPCR to determine the association of genes with HAPE susceptibility. Following are some key conclusions drawn from those studies.

Alteration in expression profile: Alteration in gene expression is of particular interest to understand the pathophysiology of HAPE that was further extended to understanding of HAPE susceptibility. Evidences suggest that there were significant differences in the expression pattern of several genes in a short hypoxia exposure as low as 3 hours [29]. Many genes associated with the antioxidant capacity of cells were shown to be affected in hypoxic exposures, while in animal's brain and lung transcriptomics also showed altered expression of genes associated with vasoreconstruction and antioxidant regulation [30,31]. Another category of genes whose relationship with HAPE was elucidated to a great extent are nitric oxide synthase 3 (*NOS3*), cytochrome P450, family 11, subfamily B (*CYP11B),* angiotensin I converting enzyme *(ACE)*, heat shock protein 70 (*HSP70*), endothelin-1and pulmonary surfactant proteins A1 and ,tyrosine hydroxylase (*TH*) and vascular endothelial growth factor (*VEGF*) [32,33]. These genes are dependent upon various bio-molecules which act as mediators and bring about the physiological manifestations associated with these genes.

Recently a study at by Sharma et al. [34] showed differential expression of a large clad of genes associated with energy metabolism were altered during hypoxia and may therefore be associated to the susceptibility. Genome wide profiling associated differential regulation of OXPHOS (oxidative phosphorylation) pathways to HAPE-susceptibility.

Gene polymorphism and haplotype: Many genes and their associated polymorphisms have been implicated with HAPE incidence and progression [32,35]. Broadly, gene polymorphism associated with HAPE may be categorized into two broad groups, a) those involved in hypoxia sensing and singling, other b) those involved in vasculature and cardiopulmonary architecture.

a) Polymorphism in genes involved in hypoxia signaling: The eNOS gene product nitric oxide synthase catalyzes the synthesis of nitric oxide (NO) from L-Arginine. NO, a pulmonary vasodilator, is another crucial biomolecule to prevent over perfusion in the lungs. In fact, most studies suggest that NO synthesis or its impairment are crucial to pulmonary ventilation and blood oxygen saturation relating to HAPE pathophysiology and inhaling NO has been shown to reduce PAP, thus preventing fluid accumulation in lungs, the primary physiological event in HAPE [24-27,36]. The frequency of Glu289Asp and 27-bp VNTR (eNOS4a) was found significantly higher in HAPE-susceptible Japanese individuals [24,33]. Also, G894T, A922G and T786C polymorphisms were observed to be at a higher frequency in HAPE-susceptible individuals in another study [37]. A case-control study done in Qinghai-Tibet region consisting of railway construction workers showed that frequencies of the 894T allele and heterozygous G/T of the 894G/T variant were significantly higher in HAPE patients as were the two haplotypes-T-T-5 repeats of 27 bp VNTR and C-G-4 repeats of 27-bp VNTR [25]. Although a few studies have stated that there is no conclusive evidence to associate eNOS gene polymorphisms to HAPE-susceptibility, most of these studies suffer from drawbacks in experimental design, e.g. small and variable sample populations [33].

AT1R (Ang II type 1 receptor) has been found to be associated with increased vascular resistance leading to increased PAP. G1517T, an AT1R polymorphism has been reported to cause susceptibility to HAPE. Hotta et al. [18] have hypothesized that AT1R polymorphisms, not ACE-I/D genotype, might be associated with HAPE-susceptibility in Japanese populations [17].

Three single nucleotide polymorphisms (SNPs) in adrenergic receptor (ADRB2) have been shown to associate with HAPE were, 46A/G, 79C/G and 523C/A. Of these, haplotypes from 46A/G and 79C/G SNPs have been found to be strongly associated with HAPE and show greater power in predicting HAPE. The haplotype 46G_79C_523C has been significantly overrepresented in HAPE-resistant individuals [38].

Surfactant protein A (SP-A) is a type of pattern recognition molecule of the collectin family of C-type lectins. Being a part of innate immune system, it regulates macrophages and protects against damage from an overzealous inflammatory response [39]. SP-A is of two types-SP-A1 and SP-A2. It has been observed that 1101 T, 3192C, 3234C alleles of SP-A1 and SP-A2 allele 3265C were associated with HAPE-susceptibility [40].

In a study correlating *HSP70* genes (hsp-70-1, hsp-70-2, hsp-70-hom) with a risk of developing high-altitude illness, it was found that individuals carrying the genotypes hsp70-2 B/B and hsp70-hom A/B and B/B might be susceptible, while individuals with the hsp70-hom A/B genotype may be tolerant to high-altitude illnesses [41]. Another study on Chinese railway construction workers found that haplotype Hap 4 (G–C–A, in order of rs1061581, rs1043618 and rs1008438) and Hap 5 (G–G–A) had an 86% reduced risk, whereas Hap 7 (A–C–C) had a 2.43-fold increased risk for HAPE. The diplotype, Dip 5 (Hap1–Hap7) was also reported to have an increased susceptibility to HAPE [15]. Also, rs1061581, rs1043618 and rs1008438 polymorphisms within Hsp70 family caused HAPE-susceptibility in Chinese with polymorphism rs1008438 causing a change in *HSPA1A* promoter activity and potentially leading to HAPE development [15]. *HSP1A* and *HSP1B* genes have also been found to be associated with HAPE-susceptibility [14].

EPAS-1 is an oxygen sensor capable of integrating cardiovascular function, energetic demand, muscular activity and oxygen availability into a physiological adaptation. Dominant endothelial PAS domain protein 1 (*EPAS-1*) haplotype (A/rs13419896-G/rs4953354-A/rs4953388) have been found in Sherpas and Tibetans but the SNPs were reversed in non-sherpa lowlanders [17]. This specific *EPAS-1* haplotype provides an adaptive advantage to Sherpas and Tibetans. *EPAS-1* encodes HIF-2A which acts upon many hypoxia inducible genes mainly regulating erythropoietin gene. *EPAS-1* can also directly bind to *VEGF* promoter, suggesting a role of VEGF in endothelial functions during HAPE [33].

EGLN-1 (Egl 9 homolog 1), well known cellular oxygen sensors are generally inactivated by hypoxia, ceasing the ubiquitination of HIF-1α and resulting in the formation of a stable functional *HIF-1* protein marshalling hypoxia-adaptive responses [42]. Thus, *EGLN-1* and *HIF-1* are inversely related. But TT genotype of rs479200 in *EGLN-1* gene is associated with HAPE-susceptibility as it increases the levels of *EGLN-1* [33] EGLN-3 levels are also elevated in HAPE. It contributes to HIF-2A stability and regulation. *EGLN-3* inhibits HIF-2α modulated hypoxia responsive elements [34]. As evident from previous studies that mitochondria plays a role in HAPE susceptibility the mitochondrial haplotype has also been found associated with susceptibility. Luo et al. [16] found that in Han Chinese mitochondrial haplogroups D4 and B4b confer HAPE-resistance whereas haplogroups B in general and haplogroups B4c in particular cause HAPE-susceptibility. Based on this information it is difficult to remark conclusively on the exact array of genes that directly influence the HAPE susceptibility. Oxygen sensing

itself is not well understood and therefore more knowledge needed to acquire by scientific studies in terms of genome wide expression analysis and also the polymorphism studies involving different ethnic groups and clads originally living at high altitudes.

b) Polymorphism of the genes involved in vasculature architecture: The Renin-Angiotensin-Aldosterone System (RAAS) a known signaling pathway favoring vasopressors causing overperfusion has also been scrutinized. Renin converts angiotensinogen to angiotensin I (*ANG I*). Angiotensin converting enzyme (ACE) converts ANGI to the biologically active angiotensin II *(ANG II),* a potent vasopressor 10-40 times more effective than adrenalin while degrading the vasodilator bradykinin. Ang II stimulates aldosterone synthesis which is regulated by *CYP11B2*, the gene for aldosterone synthetic enzyme. Aldosterone causes renal sodium resorption and secondary fluid retention.

ACE gene has two known variants- Insertion (I) and Deletion (D) caused by the presence/absence of a 287-bp Alu repeat in intron 16. The *ACE-I* allelic variant has consistently been associated with improved performance and tolerance of high-altitude whereas the *ACE-D* variant has been shown to hamper acclimatization to high-altitude [22,43-45].

Upon a rapid ascent, hypoxemia occurs and causes enhanced activation of RAAS pathway. This leads to increased levels of the vasopressor, Ang II, and causes pulmonary vasoconstriction. The effects can be minimized if ACE activity is modulated and herein comes the I/D allelic variants can potentially play arole. Although there are conflicts as to whether *ACE-I* variant confers improved tolerance to high-altitude, *ACE-D* allele was found to be associated with an increased risk of developing HAPE [46,47]. *ACE* polymorphisms that were associated with HAPE-susceptibility included A240T and A2350G, and A344T [48]. Additionally, analysis have been reported to show C344T and K173R in cytochrome P450 family. Also, *CYP11B2* and A240T polymorphism in *ACE* have been significantly associated with HAPE [19].

Physiological responses against hypobaric hypoxia begin with changes in cardiopulmonary responses and vasculature reconstruction is one the prime feature of adaptability against hypobaric hypoxia induced stress. As most of the vascular rearrangements at molecular level intersect the VEGF signaling axis, so polymorphism in the VEGF and associated genes can be used as key to understand HAPE susceptibility. However, the amount of information on VEGF and associated polymorphism is limited and more studies especially ethic differences and natives should be evaluated to create a haplotype database and enhance the understanding.

Evidences from proteomics

Most of the proteomics information about HAPE susceptibility has come from validation of putative genomics biomarkers. Some independent proteomics studies on HAPE susceptibility that were carried by Yasmin et al. [49] were primarily from the HAPE patients but non-availability of samples from healthy, mountain-travelers and their travel record posed a difficulty in profiling susceptibility of HAPE. However some of the undermentioned proteins have emerged as putative biomarkers.

Surfactants and channel proteins: Survey on bronchoalveolar lavage (BAL) conducted by Roach RC et al. [11] showed that red blood cells and total protein concentration in the alveolar fluid were dramatically increased in HAPE-susceptible individuals compared to healthy controls at the of 4559 m whereas it was very similar at 550m. RBCs increased from 6% in controls to 71% of total BAL cells in HAPE patients. Total protein concentrations in healthy controls was 14mg/dl but went up to 163 mg/dl in HAPE patients [4]

The increased endothelin-1 (ET-1) levels causes pulmonary hypertension [33]. Endothelin converting enzyme-1 transcripts and Endothelin receptor type A regulated genes are upregulated in HAPE. Both can serve as possible biomarkers for HAPE [34]. She J et al. [32] observed that at simulated altitude of 5000 m, aquaporin 5(AQP5) knockout (AQP5-/-) mice had increased lung wet:dry weight ratio and higher protein concentrations in broncheoalveolar lavage fluid. They concluded that AQP5-knockouts had elevated edema and lung injury during HAPE.

Two of these mediators (Na^+,K^+-ATPase, ENaC) decide whether fluid accumulates or egresses from alveoli. The quantity of fluid escaping into extravascular space and the rate of its clearance by alveolar respiratory epithelium consisting of ENaC and Na^+,K^+-ATPase decide whether lungs remain clear or edema occurs [6,50]. Amiloride-sensitive sodium channel (ENaC) on the alveolar epithelial cell working in tandem with the Na^+,K^+-ATPase pump on the interstitial side (basolateral side) of the cell help to keep the alveoli dry by egressing fluid from the alveoli [3]. Na^+,K^+-ATPase activity decreased in time-dependent manner when exposed to hypoxia due to ROS formation [6]. ENaC activity also decreased due to hypoxia and hypothermia and is constitutively regulated by genetic factors [3]. The activity of these two channels was measured as a function of nasal transepithelial potential difference at inferior turbinate. It was found to be associated with the decreased amiloride-sensitive fraction, both being significantly lower in HAPE-prone individuals even at low altitude [26]. Chloride channels K (CLCNK), along with sodium channels are responsible for membrane potential stabilization and salt reabsorption in lungs [13]. Most of these channels along with transient receptor potential Ca^{2+} and K^+ cation channels, are localized in caveolae. Murray et al. [51] implicated caveolae in HAPE and observed that depletion of caveolin and/or caveolae (perhaps by statins) by virtue of reducing pulmonary vasoconstriction and protecting endothelial barrier function, may indeed be a novel treatment or prophylactic measure against HAPE.

Plasma proteins: Plasma proteomics studies carried out at the author's lab showed that during acute phase, haptoglobin, and apolipoprotein A-I were found to be overexpressed in HAPE patients compared to sea level residents [49]. During the recovery phase, apolipoprotein A-IV and serum amyloid P component was observed to be overexpressed [49,52]. Yan and coworkers suggested that proteins of the acute phase response in HAPE patients can potentially be used as biomarkers in future [52]. Furthermore, another study from our lab had indicated the increased levels of transthrytin in high altitude natives in comparison to lowlanders, which suggest the role of this protein in adaptability to high altitude [49] These results suggest the possible role of pathways directly associated with lipid transport and its metabolism and vasculature remodeling. However a connecting link between these changes is missing and more studies involving systems biology approach in HAPE and their integration could provide a better picture.

Lung tissue protein/extracellular matrix proteins: Tissue inhibitor of metalloproteinase 3 (TIMP3) binds extracellular matrix (ECM) and regulates matrix metalloproteinase activity. Impairment of TIMP3/MMP system causes pulmonary edema and inflammation with ECM loss being a striking feature. Kobayashi et al. [14] have observed that the varying conformation of these proteins due to polymorphic forms

caused variation in strength and elasticity in the pulmonary interstitial spaces of HAPE-prone and HAPE-resistant individuals. A recent study aimed at delineating the gradual and dynamic changes in pulmonary proteome during hypobaric hypoxia also provided a number of protein molecules that may be further evaluated for susceptibility testing, SULT1A1 is one of them [53].

Evidences from metabolomics

Using 1H-NMR, significant differences at a given altitude were noted between individuals with HAPE and the resistant population [54]. Twenty metabolites were found to be significantly altered in individuals with HAPE compared to control group of male Han Chinese aged 20-30 years [54]. Free amino acids valine, lysine, leucine, isoleucine, glycerylphosphorylcholine, glycine, glutamine, glutamic acid, creatinine, citrate, and methyl histidine were significantly increased in HAPE patients indicating that such individuals, amino acids were exhausted by way of dysregulated proteolysis and used for energy supplementation via gluconeogenesis [54]. Compared to the control group, Individuals with HAPE had significantly lower levels of a- and b-glucose, trimethylamine, and the metabolic products of lipids (e.g., VLDL & LDL). These factors points to a glaring ATP insufficiency in HAPE individuals, which may be conducive to HAPE progression [54]. Various putative markers for HAPE have been illustrated in Figure 1. Candidate biomolecules, genes, proteins and metabolites that have crucial roles in incidence and progression of HAPE are summarized in Table 2 below.

Diagnosis, Prophylaxis and Treatment of HAPE

Diagnosis

High altitude pulmonary edema, although specific and restricted to high altitude travelers can prove lethal, if left untreated. Timely treatment of HAPE depends on its timely diagnosis. With technological advancements and scientific knowledge about HAPE, several internationally accepted diagnosis criteria have been developed. Pennardt A [55] in a recent review on HAPE stated the early manifestations of HAPE as decreased exercise tolerance and

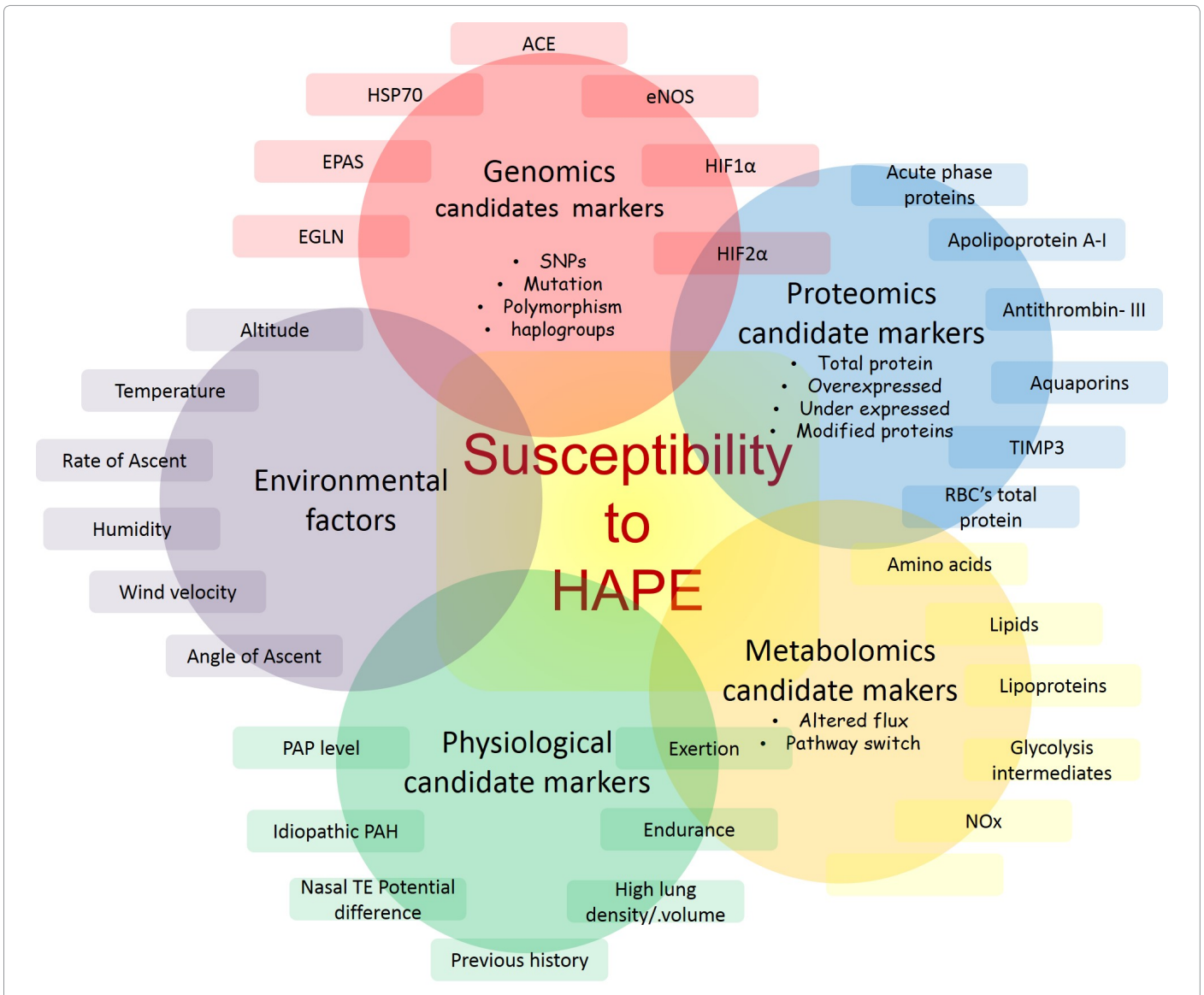

Figure 1: putative markers for HAPE.

a. Genomic markers

Genes/Pathways/Biomolecules Involved	Polymorphisms/SNPs/ Diplotype	Effects on HAPE	Ref..
Na-K ATPase, ENaC, CLNCK, Caveolae	--	Reduction of caveolae may prove to be prophylactic.	[50]
Nitric oxide synthase genes	G894T, –A 922G and –T 786C, Glu289Asp and 27-bp VNTR (eNOS4a)	Increased susceptibility.	[37]
RAAS system	ACE-I/D(27-bp intron), CYP11B2(-240AA, 2350GG and -344TT),AT1R(G1517T)	ACE-I confers adaptation, CYP11B2 polymorphisms deviating from wild type cause susceptibility, AT1R polymorphisms increase susceptibility.	[46, 47]
Hsp70 gene family	Dip5 (Hap1–Hap7),	Increased susceptibility. But wild type helps in hypoxia tolerance.	[14]
β-adrenergic receptors	haplotype 46G_79C_523C	Confers resistance.	[55]
SP-A1 & SP-A2	1101 T, 3192C, 3234C alleles of SP-A1; SP-A2 allele 3265C	Increased susceptibility.	[39]
ET-1 & ECE-1	G2288T(rs2070699)	Increased susceptibility.	[22]
EPAS-1	(A/rs13419896-G/rs4953354-A/rs4953388)	Confers resistance.	[16]
EGLN-1	TT genotype of rs479200	Increased susceptibility.	[34]
AQP5	--	Knockouts have increased lung injury and edema.	[32]
Mitochondrial haplogroups D4 & B	B4b, B4c and D4	D & B4b confers resistance and B4c increased susceptibility.	[15]
TIMP3/MMP	derived allele C of rs130293 in TIMP3 gene; haplotype CAC	Confer resistance.	[13]

b. Proteomic and Metabolomic markers

Proteins	Mechanism of Action in hypoxia	Physiological effects	
Pur-α	transcriptional activator responsible forcoordinated induction of β-2 integrin family	Pur-α expression leads to increasedangiogenesis. Also found in lungs of patients with idiopathic PAH.	[56]
Chloride intracellular channel protein-4 (CLIC-4)	supports the acidification of vacuoles along the intracellular tubulogenic pathway	May play a role in angiogenesis. Also implicated in PAH pathogenesis.	[57]
Periostin	TGF-β inducible; advances the atherosclerotic and rheumatic cardiac valve degeneration by inducing angiogenesis	Up-regulation of this protein has also been reported in patients with idiopathic PAH	[57]
Macrophage migration inhibitory factor (MIF)	one of the mediators of hypoxia-induced pulmonary hypertension	Hypoxia stimulates the expression of MIF in human vascular smooth muscles via HIF-α dependent pathway.	[58]
HSP-70	HSP-70 protects intestinal epithelial cells from hypoxia/ reoxygenation injury via a mechanism involving mitochondrial pathways	Promotes hypoxic tolerance and facilitates acclimatization to acute hypobaric hypoxia in rat and mouse models.	[59]
Rho-A	Rho-A activation promotes VEGF secretion but the activation mechanism of Rho-A not clear.	Prolonged hypoxia increases Rho-A and ROS signaling and activation in pulmonary artery smooth muscles and endothelial cells	[60]

Table 2: Summary of Putative Biomarkers for HAPE.

a prolonged recovery period after exertion at altitude. Dyspnea on exertion chest discomfort and dry cough development followed by dyspnea at rest as the disease progresses. In severe cases, blood-tinged cough, frothy sputum, tachycardia and tachypnea were observed. A low-grade fever and cyanosis, orthopnea in severe cases were observed. Some atypical forms of HAPE also prevail, especially on ascent upto 3000 meters. This atypical form of HAPE is often mis-diagnosed as other respiratory malfunctions and needs to be carefully investigated. Following are some diagnostic methods currently being used for the diagnosis of HAPE.

Sputum examination: Cough that produces frothy sputum tinged with blood is a common recognizable symptom in HAPE. Although, clinicians have used this indication for over several decades, newer methods based on the analysis of sputum needed to be developed. Sputum analysis is a noninvasive sampling technique and can be effectively used for the analysis of various airways infection. A method suggested by Pedersen et al. [56] for the analysis of cytokines and other cellular proteins in paraffin embedded sections represents excellent approach for use of sputum for HAPE diagnosis.

Chest X ray: Chest X ray is a classical diagnostic methods for detection of several pulmonary/respiratory disorders. Key observations that distinguish chest X ray of an individual with HAPE are decreased pulmonary transmittance, increased or obscure lung markings, and ground glass-like changes in the lung, or patchy shadows [4] For detailed description about radiological readers are suggested to refer an illustrated review on radiologic features of pulmonary edema [57].

CT scan: Computerized Tomography (CT) scan provides a better comprehensive detail of edema lung across the different planes. Increased and enlarged lung markings, ground glass-like changes in the lung, nodule-like shadows, scattered or isolated alveolar edema of terminal bronchioles, and slim reticulate shadows can be observed [4]. Also, airspace consolidation and subpleural airspaces may be recognized using CT scans. Widespread use of CT scan for screening for over a decade has led to the maturation of this technique in HAPE pathophysiology.

Electrocardiogram: Some important features that are often observed in electrocardiograms of individuals with HAPE are sinus tachycardia

that may suggest existence of acute pulmonary hypertension, right axis deviation, right bundle branch block and right ventricular hypertrophy by voltage (tall R wave over the right precordial leads). Furthermore, right atrial enlargement (peaked P waves in leads II, V1, and V2) were commonly observed. Hemodynamic measurements reveal high pulmonary artery pressure and pulmonary vascular resistance [55] as well as low to normal pulmonary wedge pressures, cardiac output, and systemic arterial blood pressure.

Colour doppler: Eco Doppler technique in colour mode is not only an important diagnostic tool for high altitude pulmonary odema but one can also predict susceptibility to HAPE. Vacheiery showed that hypoxia decreased the ratio of pulmonary blood flow acceleration time (AT) and peak velocity of tricuspid regurgitation jet (TR), and therefore the susceptibility could be predicted using color Doppler technique. Duplain et al. [58] demonstrated augmented sympathetic activation in HAPE susceptible subjects, while, Gruig et al. [59] used stress Doppler echocardiography for identification of susceptibility to HAPE.

Ultrasound can also reveal some of the early signs of HAPE especially based on the common scoring system called "comet tail" artifacts, these are generally produced by microreflections from interstitial or alveolar edema. Fagenholz PJ et al. [60] studied the potentials of ultrasonography to detect HAPE and shown higher scores and lower oxygen saturation in HAPE patients compared with controls. Comet tail scores decreased as HAPE cleared in these patients. Another sonography study of comet tails demonstrated a high prevalence of clinically silent interstitial edema mirrored by decreased oxygen saturation in climbers. However, comet tails alone do not guarantee clinical prevalence of HAPE and other clinical corelations must be made before completion of diagnosis.

Prophylaxis

Susceptibility to HAPE is variable among different ethnic groups and even among the individuals of the same population. HAPE can be prevented by limiting the rate of ascent above 2000 m to <350 m per day [61] and allowing an individual time to acclimatize by limiting exertion in the first few days. Avoiding alcohol and sleeping pills are also recommended [62]. Prophylactic treatment can provide handy solution. Standard methodology is to use pulmonary vasodilators that prevent the rise of PAP [61,63].

Nifedipine, a Ca^{2+} channel antagonist, acts as a vasodilator on both systemic as well as pulmonary circulation. It lowers or controls the rise in PAP. It has served as the drug of choice for prophylaxis for a long time. 20 mg Nifedipine in slow release formulation taken every 8 h should be begun 24 h before ascent and continued till descent [61]. But it may cause hypotension if taken with other medications for hypertension, e.g. α-blockers and β-blockers used for hypertension. Also in individuals with hepatic insufficiency, caution is advised. In these individuals, the dose should be halved and taken every 12 h with careful follow up of blood pressure. Use of *Gingko biloba* should be avoided with nifedipine [64].

Tadalafil (10-20 mg bids) and sildenafil (50 mg every 8 h starting 24 h before ascent), both phosphodiesterase-V inhibitors, were found to be effective as prophylactics against HAPE. Sildenafil is pulmonary vasoconstrictor and hence preferred for individuals at risk of hypotension [65]. 40 mg sildenafil taken thrice a day at 4350 m for 6 days has been shown to preserve exercise performance and limit altitude-induced hypoxemia without altering the acclimatization process [65]. The major contention against phosphodiesterase-V inhibitors is that they exacerbate AMS through unknown mechanisms [66]. Apart from this, they are to be avoided in individuals suffering from cirrhosis. Even in individuals with creatinine clearance rates of 30-50 mL/min or less, caution is advised. Patients with portal hypertension have increased risk of variceal bleeding if using sildenafil. Patients receiving nitrate containing medications for coronary artery disease or using NSAIDs must avoid use of phosphodiesterase-V inhibitors [64].

The β-agonist, Salmeterol (125 μg bids), has also shown promise as an easy to carry and use long-acting inhalant prophylactic against HAPE [62]. It improves alveolar fluid clearance in susceptible individuals [67]. But its use should be avoided in case of patients suffering from hepatic insufficiency, hypokalemia and tachyarrythmias [64]. Both tadalafil and salmeterol require further studies to gain conclusive data on their safety profiles relating to mountaineering.

Dexamethasone, a corticosteroid proven effective against AMS, also prevents HAPE when taken 1 day prior to ascent and continued till descent [62]. The dosage is 4-8 mg every 12 h till descent when ascending at a rate of >1000 m/day for <5 days. Co-administering with sildenafil helps to prevent both HAPE and AMS [63]. The PAP-lowering effect of dexamethasone can be attributed to the following mechanisms: (a) stimulation of cGMP production in hypoxia (b) increased activity of NOS genes (c) modulation of sympathetic activity (d) improving pulmonary transepithelial Na^+ and water transport (e) improved surfactant production (f) tightening of pulmonary capillary endothelium by possible inhibition of inflammatory mechanism [63]. Dexamethasone is not an option for patients suffering from amoebiasis, strongyloidiasis, active peptic ulcer disease and upper-GI tract bleeding. Concurrent use of alcohol and NSAIDs should be avoided. Dexamethasone should never be abruptly stopped at altitude as it doesn't facilitate acclimatization but it has recently been shown to improve exercise performance in HAPE-prone individuals [68].

Acetazolamide, a carbonic anhydrase inhibitor which blocks out pulmonary vasoconstriction and used as the mainstay drug in cases of AMS and HACE, has anecdotally been proven beneficial in preventing HAPE but in individuals with renal insufficiency and failure the drug should either be given at lower dosages with longer time-intervals or completely avoided. Same is true for patients with pre-existing acidosis, sulfa-allergy and liver disease [64].

Treatment

HAPE is curable and rapid recovery is a rule in any therapeutic intervention. Clinical case studies and research over decades have established descent to lower altitude as the best possible measure to ameliorate the progression of HAPE and complete recovery. However other therapeutic interventions are routinely being sought by researchers as rapid descent may not always be possible in rough terrains and can be lethal in conditions like HAPE. Following three approaches are generally suggested for management of HAPE, and are being used alone or in combination.

Immediate descent: The most reliable and effective treatment for HAPE is immediate descent to a lower altitude, at least by 1,000 m (approximately 3,280 ft). Descent should be gradual and passive, since physical exertion is likely to exacerbate the patient's condition [69]. As high altitudes are colder and such conditions promote vasoconstriction, keeping the patient warm will minimize cold-induced sympathetic contribution to HAPE [70]. If means of transportation are not available or patient is unable to descent simulated descent may be observed using hyperbaric chambers eg a portable hyperbaric chamber (e.g., HyperOxy, Solace 210, Repiro 270, Vitaeris 320, GamowA bag, CertecA bag, and PACA) can be used at 2 to 4 lb/inch^2 for several hours [71] to simulate a descent of 1,500 m or more. Continuous positive airway

pressure (CPAP) is another useful strategy that operates on the principle of maintaining a continuous positive airway pressure (CPAP) in a spontaneously breathing patient. It is functionally similar to positive end-expiratory pressure (PEEP). Foti et al. [72] showed that CPAP based helmets could be an effective first line pre-hospital treatment for presumed severe high altitude pulmonary edema [73].

Oxygen supplementation: If evacuation to a lower altitude is unsafe or impossible then oxygenation strategies may offer immediate support to the patient. The improved arterial oxygen saturation tends to decrease pulmonary hypertension and vasoconstriction and subsequently the extravascular fluid accumulation. The treatment of pulmonary edema began even before it was understood explicitly. Early attempts at treatments during 1930-40s focused on various contraptions which could provide positive pressure oxygen/air to improve oxygenation and alleviate distress [74]. Moving to more recent trends regarding treatment of HAPE, one finds the onus to have shifted to supplemental oxygen therapy (4-6 l/min) and immediate rapid descent of about 500-1000 m followed by bed rest and avoidance of cold. Inhalation of nitric oxide (40ppm for 15 minutes) improved oxygenation in HAPE-patients but had the reverse effect on the HAPE-resistant controls [36]. Administering nitric oxide directly at high-altitude could be unfeasible but use of L-Arginine supplements seems an easy way out as L-Arginine is a precursor of nitric oxide [6].

Pharmacological intervention: When immediate descent or oxygen supplementation is not possible, treatment with nifedipine (20 mg slow release, taken every 6 h) or sildenafil or using hyperbaric chamber are enough to alleviate HAPE within 24-48 h. However, drug use is mostly not necessary as treatment with supplementary oxygen and bed rest are generally enough for recovering from HAPE [62,63]. A recent therapeutic modality, nitric oxide supplemented was augmented and an efficient delivery system was developed *en house* [75]. Common therapeutic drugs are summarized in Table 3.

Conclusion and Future Directions

Plethora of scientific information is now available on diagnosis and therapy of HAPE and if detected on time it is curable, yet we do not

Proteins	Mechanism of Action in hypoxia	Physiological effects	Ref
Pur-α	transcriptional activator responsible forcoordinated induction of β-2 integrin family	Pur-α expression leads to increasedangiogenesis. Also found in lungs of patients with idiopathic PAH.	[56]
Chloride intracellular channel protein-4 (CLIC-4)	supports the acidification of vacuoles along the intracellular tubulogenic pathway	May play a role in angiogenesis. Also implicated in PAH pathogenesis.	[57]
Periostin	TGF-β inducible; advances the atherosclerotic and rheumatic cardiac valve degeneration by inducing angiogenesis	Up-regulation of this protein has also been reported in patients with idiopathic PAH	[57]
Macrophage migration inhibitory factor (MIF)	one of the mediators of hypoxia-induced pulmonary hypertension	Hypoxia stimulates the expression of MIF in human vascular smooth muscles via HIF-α dependent pathway.	[58]
HSP-70	HSP-70 protects intestinal epithelial cells from hypoxia/ reoxygenation injury via a mechanism involving mitochondrial pathways	Promotes hypoxic tolerance and facilitates acclimatization to acute hypobaric hypoxia in rat and mouse models.	[59]
Rho-A	Rho-A activation promotes VEGF secretion but the activation mechanism of Rho-A not clear.	Prolonged hypoxia increases Rho-A and ROS signaling and activation in pulmonary artery smooth muscles and endothelial cells	[60]

Table 3: Common therapeutic applications for HAPE.

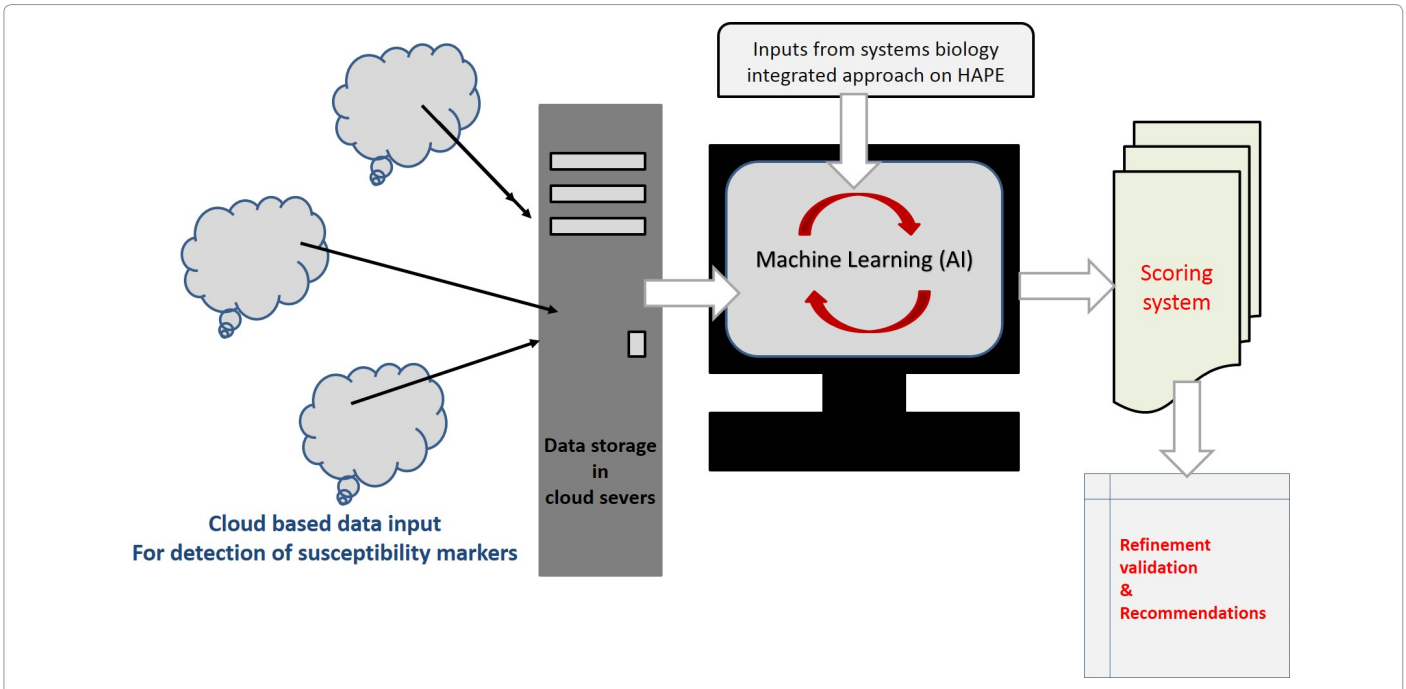

Figure 2: HAPE susceptibility scoring based on the machine learning or artificial intelligence

have a precise answer for HAPE susceptibility. Involvement of genetic, epigenetic, physiological and other associated factors in deciding the HAPE susceptibility poses a major challenge for the scientific resolution of the problem. With the advancement and accessibility to high throughput omics technologies, genome-wide data sets and description of susceptibility architecture, translational research in high altitude medicine will be an important aspect of medical progress [34]. Global metabolite profiling combined with a systems biology approach (i.e., integrating genomics, epigenomics, and proteomics) is an exciting upcoming approach for improving our understanding of HAPE and evaluating various potential biomarkers for the same. As a futuristic vision, developments in modelling of computer simulations of various biological networks to investigate "what if" questions about real world systems may provide implantable solution for susceptibility assessment. Furthermore, this could be extended to cloud based screening of aforesaid biomarkers and development of HAPE susceptibility scoring based on the machine learning or artificial intelligence, where the clinicians and researchers across the globe may be brought together on same platform and allowed to feed their observations in cloud servers, wherein using artificial intelligence and machine learning a suitable scoring system can be developed for redefining susceptibility. The hypothetical view of this concept is illustrated in Figure 2.

Acknowledgement

Authors would like to acknowledge Director, Defence Institute of Physiology and Allied Sciences (DIPAS, DRDO) for funding past project reported in this study. Authors thank Dr. Soma Sarkar for critically reviewing the manuscript and suggesting improvements. Aditya Arya is a recipient of Senior Research Fellowship (SRF) and Subhojit Paul is recipient of Junior Research Fellowship from Council of Scientific and Industrial Research (CSIR), Government of India. Anamika Gangwar is recipient of INSPIRE- Junior Research Fellowship from Department of Science and Technology, Government of India.

References

1. Paralikar SJ, Paralikar JH (2010) High-altitude medicine. Indian J Occup Environ Med 14: 6-12.
2. Bärtsch P (1993) Acute mountain sickness and high altitude pulmonary edema. Dtsch Med Wochenschr 118: 1463-1464.
3. Basnyat B (2005) High altitude cerebral and pulmonary edema. Travel Med Infect Dis 3: 199-211.
4. Bärtsch P, Mairbäurl H, Maggiorini M, Swenson ER (2005) Physiological aspects of high-altitude pulmonary edema. J Appl Physiol (1985) 98: 1101-1110.
5. Basnyat B, Murdoch DR (2003) High-altitude illness. Lancet 361: 1967-1974.
6. Schoene RB (2004) Unraveling the mechanism of high altitude pulmonary edema. High Alt Med Biol 5: 125-135.
7. Bouzat P, Walther G, Rupp T, Doucende G, Payen JF, et al. (2013) Time course of asymptomatic interstitial pulmonary edema at high altitude. Respiratory Physiology & Neurobiology 186: 16-21.
8. Cremona G, Asnaghi R, Baderna P, Brunetto A, Brutsaert T, et al. (2002) Pulmonary extravascular fluid accumulation in recreational climbers: a prospective study. Lancet 359: 303-309.
9. Mortimer H, Patel S, Peacock AJ (2004) The genetic basis of high-altitude pulmonary oedema. Pharmacol Ther 101: 183-192.
10. Sartori C, Vollenweider L, Löffler BM, Delabays A, Nicod P, et al. (1999) Exaggerated endothelin release in high-altitude pulmonary edema. Circulation 99: 2665-2668.
11. Swenson ER, Maggiorini M, Mongovin S, Gibbs JS, Greve I, et al. (2002) Pathogenesis of high-altitude pulmonary edema: inflammation is not an etiologic factor. JAMA 287: 2228-2235.
12. Roach RC, Bartsch P, Hackett PH, Oelz O (1993) Lake Louise acute mountain sickness scoring system. Burlington: Queen City Press.
13. Carter EA, Mayo JR, MacInnis MJ, McKenzie DC, Koehle MS (2014) Individual susceptibility to high altitude and immersion pulmonary edema and pulmonary lymphatics. Aviat Space Environ Med 85: 9-14.
14. Kobayashi N, Hanaoka M, Droma Y, Ito M, Katsuyama Y, et al. (2013) Polymorphisms of the tissue inhibitor of metalloproteinase 3 gene are associated with resistance to high-altitude pulmonary edema (HAPE) in a Japanese population: a case control study using polymorphic microsatellite markers. PloS one 8: e71993.
15. Qi Y, Niu WQ, Zhu TC, Liu JL, Dong WY, et al. (2009) Genetic interaction of Hsp70 family genes polymorphisms with high-altitude pulmonary edema among Chinese railway constructors at altitudes exceeding 4000 meters. Clin Chim Acta 405: 17-22.
16. Luo YJ, Gao WX, Li SZ, Huang XW, Chen Y, et al. (2012) Mitochondrial haplogroup D4 confers resistance and haplogroup B is a genetic risk factor for high-altitude pulmonary edema among Han Chinese. Genet Mol Res 11: 3658-3667.
17. Hanaoka M, Droma Y, Basnyat B, Ito M, Kobayashi N, et al. (2012) Genetic variants in EPAS1 contribute to adaptation to high-altitude hypoxia in Sherpas. PLoS One 7: e50566.
18. Hotta J, Hanaoka M, Droma Y, Katsuyama Y, Ota M, et al. (2004) Polymorphisms of renin-angiotensin system genes with high-altitude pulmonary edema in Japanese subjects. Chest 126: 825-830.
19. Qi Y, Niu W, Zhu T, Zhou W, Qiu C (2008) Synergistic effect of the genetic polymorphisms of the renin-angiotensin-aldosterone system on high-altitude pulmonary edema: a study from Qinghai-Tibet altitude. Eur J Epidemiol 23: 143-152.
20. Luo Y, Wang Y, Lu H, Gao Y (2014) 'Ome' on the range: update on high-altitude acclimatization/adaptation and disease. Mol Biosyst 10: 2748-2755.
21. Clarenbach CF, Senn O, Christ AL, Fischler M, Maggiorini M, et al. (2012) Lung function and breathing pattern in subjects developing high altitude pulmonary edema. PLoS One 7: e41188.
22. Charu R, Stobdan T, Ram RB, Khan AP, Qadar Pasha MA, et al. (2006) Susceptibility to high altitude pulmonary oedema: role of ACE and ET-1 polymorphisms. Thorax 61: 1011-1012.
23. Colice GL, Lee YJ, Chen J, Du HK, Ramirez G, et al. (1995) Susceptibility to high-altitude pulmonary edema in Madison and Hilltop rats. I. Ventilation and fluid balance. J Appl Physiol (1985) 78: 2279-2285.
24. Droma Y, Hanaoka M, Ota M, Katsuyama Y, Koizumi T, et al. (2002) Positive association of the endothelial nitric oxide synthase gene polymorphisms with high-altitude pulmonary edema. Circulation 106: 826-830.
25. Yu-jing S, Ming-wu F, Wen-quan N, Guang-ping L, Jing-liang L, et al. (2010) Endothelial nitric oxide synthase gene polymorphisms associated with susceptibility to high altitude pulmonary edema in Chinese railway construction workers at Qinghai-Tibet over 4 500 meters above sea level. Chin Med Sci J 25: 215-221.
26. Sartori C, Duplain H, Lepori M, Egli M, Maggiorini M, et al. (2004) High altitude impairs nasal transepithelial sodium transport in HAPE-prone subjects. Eur Respir J 23: 916-920.
27. Busch T, Bartsch P, Pappert D, Grunig E, Hildebrandt W, et al. (2001) Hypoxia decreases exhaled nitric oxide in mountaineers susceptible to high-altitude pulmonary edema. Am J Respir Crit Care Med 163: 368-373.
28. Dehnert C, Luks AM, Schendler G, Menold E, Berger MM, et al. (2010) No evidence for interstitial lung oedema by extensive pulmonary function testing at 4,559 m. Eur Respir J 35: 812-820.
29. Arya A, Meena R, Sethy NK, Das M, Sharma M, et al. (2015) NAP (davunetide) protects primary hippocampus culture by modulating expression profile of antioxidant genes during limiting oxygen conditions. Free Radic Res 49: 12.
30. Arya A, Sethy NK, Singh SK, Das M, Bhargava K (2013) Cerium oxide nanoparticles protect rodent lungs from hypobaric hypoxia-induced oxidative stress and inflammation. Int J Nanomedicine 8: 4507-4520.
31. Sethy NK, Singh M, Kumar R, Illavazhagan G, Bhargava K (2011) Upregulation of transcription factor NRF2-mediated oxidative stress response pathway in rat brain under short-term chronic hypobaric hypoxia. Funct Integr Genomics 11: 19.
32. She J, Bi J, Tong L, Song Y, Bai C (2013) New insights of aquaporin 5 in the

pathogenesis of high altitude pulmonary edema. Diagn Pathol 8: 193.

33. Luo Y, Zou Y, Gao Y (2012) Gene polymorphisms and high-altitude pulmonary edema susceptibility: a 2011 update. Respiration 84: 155-162.

34. Sharma M, Singh SB, Sarkar S (2014) Genome wide expression analysis suggests perturbation of vascular homeostasis during high altitude pulmonary edema. PLoS One 9: e85902.

35. Luo Y, Chen Y, Zhang Y, Zhou Q, Gao Y (2012) Association of endothelial nitric oxide synthase (eNOS) G894T polymorphism with high altitude pulmonary edema susceptibility: a meta-analysis. Wilderness Environ Med 23: 270-274.

36. Scherrer U, Vollenweider L, Delabays A, Savcic M, Eichenberger U, et al. (1996) Inhaled nitric oxide for high-altitude pulmonary edema. N Engl J Med 334: 624-629.

37. Ahsan A, Mohd G, Norboo T, Baig MA, Pasha MA (2006) Heterozygotes of NOS3 polymorphisms contribute to reduced nitrogen oxides in high-altitude pulmonary edema. Chest 130: 1511-1519.

38. Stobdan T, Kumar R, Mohammad G, Thinlas T, Norboo T, et al. (2010) Probable role of beta2-adrenergic receptor gene haplotype in high-altitude pulmonary oedema. Respirology 15: 651-658.

39. Pastva AM, Wright JR, Williams KL (2007) Immunomodulatory roles of surfactant proteins A and D: implications in lung disease. Proc Am Thorac Soc 4: 252-257.

40. Saxena S, Kumar R, Madan T, Gupta V, Muralidhar K, et al. (2005) Association of polymorphisms in pulmonary surfactant protein A1 and A2 genes with high-altitude pulmonary edema. Chest 128: 1611-1619.

41. Zhou F, Wang F, Li F, Yuan J, Zeng H, et al. (2005) Association of hsp70-2 and hsp-hom gene polymorphisms with risk of acute high-altitude illness in a Chinese population. Cell Stress Chaperones 10: 349-356.

42. Hackett PH, Roach RC, Hartig GS, Greene ER, Levine BD (1992) The effect of vasodilators on pulmonary hemodynamics in high altitude pulmonary edema: a comparison. Int J Sports Med 13 Suppl 1: S68-71.

43. Woods DR, Humphries SE, Montgomery HE (2000) The ACE I/D polymorphism and human physical performance. Trends Endocrinol Metab 11: 416-420.

44. Woods DR, World M, Rayson MP, Williams AG, Jubb M, et al. (2002) Endurance enhancement related to the human angiotensin I-converting enzyme I-D polymorphism is not due to differences in the cardiorespiratory response to training. Eur J Appl Physiol 86: 240-244.

45. Patel S, Woods DR, Macleod NJ, Brown A, Patel KR, et al. (2003) Angiotensin-converting enzyme genotype and the ventilatory response to exertional hypoxia. Eur Respir J 22: 755-760.

46. Dehnert C, Weymann J, Montgomery HE, Woods D, Maggiorini M, et al. (2002) No association between high-altitude tolerance and the ACE I/D gene polymorphism. Med Sci Sports Exerc 34: 1928-1933.

47. Kumar R, Pasha Q, Khan AP, Gupta V (2004) Renin angiotensin aldosterone system and ACE I/D gene polymorphism in high-altitude pulmonary edema. Aviat Space Environ Med 75: 981-983.

48. Rajput C, Arif E, Vibhuti A, Stobdan T, Khan AP, et al. (2006) Predominance of interaction among wild-type alleles of CYP11B2 in Himalayan natives associates with high-altitude adaptation. Biochem Biophys Res Commun 348:735-740.

49. Ahmad Y, Shukla D, Garg I, Sharma NK, Saxena S, et al. (2011) Identification of haptoglobin and apolipoprotein A-I as biomarkers for high altitude pulmonary edema. Funct Integr Genomics 11: 407-417.

50. Scherrer U, Rexhaj E, Jayet PY, Allemann Y, Sartori C (2010) New insights in the pathogenesis of high-altitude pulmonary edema. Prog Cardiovasc Dis 52: 485-492.

51. Murray F, Insel PA, Yuan JX (2006) Role of O(2)-sensitive K(+) and Ca(2+) channels in the regulation of the pulmonary circulation: potential role of caveolae and implications for high altitude pulmonary edema. Respir Physiol Neurobiol 151: 192-208.

52. Yang Y, Ma L, Guan W, Wang Y, Du Y, et al. (2014) Differential plasma proteome analysis in patients with high-altitude pulmonary edema at the acute and recovery phases. Exp Ther Med 7: 1160-1166.

53. Ahmad Y, Sharma NK, Ahmad MF, Sharma M, Garg I, et al. (2015) The proteome of Hypobaric Induced Hypoxic Lung: Insights from Temporal Proteomic Profiling for Biomarker Discovery. Scientific Reports.

54. Luo Y, Zhu J, Gao Y (2012) Metabolomic analysis of the plasma of patients with high-altitude pulmonary edema (HAPE) using 1H NMR. Mol Biosyst 8: 1783-1788.

55. Pennardt A (2013) High-altitude pulmonary edema: diagnosis, prevention, and treatment. Curr Sports Med Rep 12: 115-119.

56. Pedersen F, Marwitz S, Seehase S, Kirsten AM, Zabel P, et al. (2013) HOPE-preservation of paraffin-embedded sputum samples--a new way of bioprofiling in COPD. Respir Med 107: 587-595.

57. Gluecker T, Capasso P, Schnyder P, Gudinchet F, Schaller MD, et al. (1999) Clinical and radiologic features of pulmonary edema. Radiographics 19:1532-1533.

58. Duplain H, Vollenweider L, Delabays A, Nicod P, Bartsch P, et al. (1999) Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. Circulation 99: 1713-1718.

59. Grünig E, Mereles D, Hildebrandt W, Swenson ER, Kübler W, et al. (2000) Stress Doppler echocardiography for identification of susceptibility to high altitude pulmonary edema. J Am Coll Cardiol 35: 980-987.

60. Fagenholz PJ, Gutman JA, Murray AF, Noble VE, Thomas SH, et al. (2007) Chest ultrasonography for the diagnosis and monitoring of high-altitude pulmonary edema. Chest 131: 1013-1018.

61. Bärtsch P, Maggiorini M, Ritter M, Noti C, Vock P, et al. (1991) Prevention of high-altitude pulmonary edema by nifedipine. N Engl J Med 325: 1284-1289.

62. Maggiorini M (2006) High altitude-induced pulmonary oedema. Cardiovasc Res 72: 41-50.

63. Maggiorini M (2010) Prevention and treatment of high-altitude pulmonary edema. Prog Cardiovasc Dis 52: 500-506.

64. Luks AM, Swenson ER (2008) Medication and dosage considerations in the prophylaxis and treatment of high-altitude illness. Chest 133: 744-755.

65. Richalet JP, Gratadour P, Robach P, Pham I, Déchaux M, et al. (2005) Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. Am J Respir Crit Care Med 171: 275-281.

66. Maggiorini M, Brunner-La Rocca HP, Peth S, Fischler M, Böhm T, et al. (2006) Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. Ann Intern Med 145: 497-506.

67. Sartori C, Allemann Y, Duplain H, Lepori M, Egli M, et al. (2002) Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med 346: 1631-1636.

68. Fischler M, Maggiorini M, Dorschner L, Debrunner J, Bernheim A, et al. (2009) Dexamethasone but not tadalafil improves exercise capacity in adults prone to high-altitude pulmonary edema. Am J Respir Crit Care Med 180: 346-352.

69. West JB (2005) The physiologic basis of high-altitude diseases. Ann Intern Med 141: 789-800.

70. Bärtsch P, Swenson ER, Maggiorini M (2001) Update: High altitude pulmonary edema. Adv Exp Med Biol 502: 89-106.

71. http://www.portable-hyperbaric-chambers.com/

72. Foti G, Sangalli F, Berra L, Sironi S, Cazzaniga M, et al. (2009) Is helmet CPAP first line pre-hospital treatment of presumed severe acute pulmonary edema? Intensive care medicine 35: 656-662.

73. Bellani G, Foti G, Spagnolli E, Castagna L, Patroniti N, et al. (2009) An improved Boussignac device for the delivery of non-invasive CPAP: the SUPER-Boussignac. Intensive Care Med 35: 1094-1099.

74. Barach AL, Molomut N (1942) An Oxygen mask metered for positive pressure. Ann Intern Med 17:820-822.

75. Himashree G, Chattopadhyay PK, Selvamurthy W (2003) Indigenisation of Nitric oxide therapy for treatment of HAPE. Delhi Tata McGraw Hill, New Delhi.