Risk factors underlying high-altitude pulmonary edema in the Ecuadorian Andes

Karen Sánchez

University Yachay Tech: Universidad Yachay Tech

Wilfre Machado

University Yachay Tech: Universidad Yachay Tech

Anita Villafuerte

IESS: Instituto Ecuatoriano de Seguridad Social

Santiago Ballaz (✉ sballazg@gmail.com)

University Yachay Tech: Universidad Yachay Tech <https://orcid.org/0000-0001-5878-8679>

Research Article

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Abstract

Background

Ascent to high altitude (> 2500 m) exposes people to hypobaric atmospheric pressure and blood hypoxemia. It provokes a syndrome whose symptoms vary from the mild acute mountain sickness (AMS) to the life-threatening, high-altitude pulmonary edema (HAPE). This study analyzed the risk for developing high-altitude sickness in a group of HAPE patients (n = 59), which was contrasted against a group of AMS patients (n = 240) as the NO HAPE group, after sojourning above 4,000 m height. The objective of this retrospective was to analyse the factors contributing to the HAPE prevalence among travellers and dwellers of the Ecuadorian Andes.

Methods

AMS and HAPE groups were compared through demographic (ethnicity, sex, and age), environmental (permanent residence altitude and recent stay at sea-level), health status (vital signs), and blood analysis variables. The Cramer's V, simple logistic regression (SLR), and multiple logistic regression (MLR) analyses revealed patterns of significant associations.

Results

Analyses revealed that high-altitude indigenous residents were HAPE-prone, while mestizos living at sea level only had AMS. Blood pressure played a role in HAPE risk. Women were more tolerant to HAPE than men. Among *indigenes*, HAPE prevalence significantly rose after sojourning at sea level, a phenomenon called "reentry HAPE".

Conclusions

In Andean *indigenes*, HAPE could be produced by a poor adaptation to high altitude, a high haemoglobin, and a blunted reactivity of blood pressure to environmentally-induced hypoxia. All the above gives support to the complex gene-environment interactions in the progress of HAPE, which may give some clues about the etiopathogenesis of non-cardiogenic edema.

1. Introduction

The term high-altitude illness (HAI), or simply *mountain sickness*, is commonly used to describe a series of cerebral and pulmonary syndromes that develop shortly after rapid ascent above 2,500 m (HA), where the atmospheric and inspired partial O₂ pressures drop down to 75% [1]. The significant reduction of the partial O₂ atmospheric pressure leads to its poor diffusion from the alveolar air into the blood, while the

percentage of O₂ carried out by hemoglobin drops down below 90% (hypoxemia). Under such hypobaric atmospheric conditions, the human body reacts by a series of mechanisms, known as acclimatization, to compensate the desaturation of blood O₂. The acclimatization process takes from hours to days, and even weeks [2]. A failure in acclimatization causes HAs [3, 4], whose symptoms and severity vary across individuals from the benign, self-limiting acute mountain sickness or AMS, to more serious clinical manifestations like the high-altitude pulmonary edema or HAPE [1] and eventually the high-altitude cerebral edema or HACE [3].

HAPE is a life-threatening condition [1] produced by a rapid accumulation of extravascular fluid flooding the pulmonary alveoli [5, 6]. However, the precise pathophysiology of HAPE is not well understood [7–11]. An exaggerated increase in the hypoxic pulmonary artery and pulmonary capillary pressure in conjunction with an uneven hypoxic pulmonary vasoconstriction are pivotal in its pathogenesis [8, 12, 13]. Antecedents of high-altitude related pulmonary illnesses increase the risk for HAPE [4, 6, 12, 14], thus pointing to genetic factors [15–17]. HAPE is a condition that could also happen at moderate altitudes [18].

Evolutionarily, Andeans have developed physiological strategies that are different from Ethiopians and Himalayans to adapt to high-altitude-induced hypoxic environments [19, 20]. Thus, an hemoglobin content above normal average is thought to represent an ideal adaptation to high altitude in Andean dwellers [21–23]. Of note, the Andes is the region with the highest HAPE prevalence worldwide [15–24]. We investigated risk factors for HAPE in an elevation of 4,000 m above sea level in the Ecuadorian Andes, where atmospheric pressure decreases to levels of 60%. Two groups of patients suffering from either HAPE or AMS (the NO HAPE group) after sojourning at 3,600–4,400 m height, were retrospectively compared using statistical association analyses of the demographic, environmental, health, and blood tests variables. A more advanced statistical analysis allowed us to explore the relative influence of the risk factors in HAPE susceptibility. Finally, a model for the most representative variables was constructed to fit their contribution to HAPE risk.

2. Methods

2.1. Study zone

This was a single-centre observational study conducted in the Claudio Benati Hospital in Zumbahua (Ecuador), a remote Andean town sited at 3,600 m height above sea level. Low-altitude and high-altitude residents frequently commute between the coast and the Andes ridge by car in this zone, through the only road connecting the Pacific coast with the Andes, which overcomes a 4,000 m slope in a 2-h ride. Given that the closest hospital was 64 Km away, chances were high that, among the visitors sojourning at very high altitude (100,000 per year), and local dwellers (approx. 20,000), those afflicted by HAI had to rush to the emergency room of the Claudio Benatí hospital.

2.2. Ethics statement

Written informed consent was waived due to the retrospective nature of the study. We followed STROBE guidelines to report this study, which was approved by the Ethics Committee of the Claudio Benatí Hospital. The authors declare they had no access to identifying patient information when analysing the data.

2.3. Diagnosis

AMS and HAPE clinical evaluations were recorded by qualified medical staff serving people permanently living at high altitude. AMS patients showed unequivocal symptoms of HAI (headache, lassitude, fatigue, dizziness, nausea, and vomiting) associated with a rapid ascent above 4,000 m height [25]. None of the AMS patients had conclusive symptoms of HACE. As to HAPE, the diagnosis relied on the examination of the cardinal symptoms including dyspnea at rest, tachypnea, crackles, wheezing; dry cough, weakness, chest tightness, and tachycardia [5], as well as on chest X-ray exams showing central interstitial edema with peribronchial cuffing, ill-defined vessels, and a patchy pattern of airspace consolidation. In this respect, patchy opacities produced by HAPE disappeared within days after receiving treatment [26].

2.4. Data collection and categorization

The database was extracted from patient files dated from the years 2007 to 2018 and kept in logbooks, conforming to a non-probabilistic sampling. Consistency between physical and digital records was meticulously checked to avoid transcription errors. The terms of the study were defined as follows:

2.4.1 Demographic variables: ethnicity was categorized as *indigenes* or *mestizo*; sex as male or female; and age classified in children (0–14 years), young (15–25 years), adult (26–64 years), and elder (≥ 65 years) according to the Statistics from Canada and the American Cancer Society [27]. The terms *indigene* and *mestizo* defined the *Panzaleo* pedigree and the mixed-race (like most of the Ecuadorians) respectively.

2.4.2 Environmental variables: residence at either high altitude (from 2,700 m to 4,400 m above sea level) or at low altitude (< 100 m above sea level); a recent stay at low altitude, categorized as either *sea level-trip* or no *sea level-trip* antecedent within the last 7 days. The term *sea level-trip* was coined to identify reentry-HAPE cases.

2.4.3 Health-status (vital signs) variables: systolic, diastolic, medium, and pulse (systolic minus diastolic) blood pressures, heart rhythm and breathing rate, blood O₂ saturation, and axillary temperature. To capture inter-individual differences in vital signs, data were allotted to low, normal, and high categories based on the reference values published by the REAL First Aid Ltd [28].

2.4.4 Blood tests: counts of red, white blood cells, and platelets per liter, concentration of hemoglobin, and hematocrit percentage. Blood counts were grouped as low, normal, and high according to the referential values reported by the Marshfield Labs and Alberta Health Service [29, 30].

2.5. Statistics

Analyses were computed using the SPSS software (Version 22) for Windows. Multiple *a priori* Student *t*-tests were applied to compare variables between the HAPE and NO HAPE (AMS) groups. After categorization of the risk factors, ordinal and nominal variables of HAPE and NO HAPE (AMS) groups were compared by contingency tables and their associations computed by the Cramer's V analysis [31]. Odds ratios (ORs) were calculated using a simple logistic regression analysis [32]. The multiple logistic regression analysis [33] was run to estimate the likelihood of HAPE on a multiple variable basis. Alpha value was set at 0.05.

3. Results

3.1. Survey of clinical archives

From a total of 1,336 patients scrutinized, 299 were admitted in the emergency room with evident symptoms of HAI after sojourning at 3,600-4,400 m height soon after arrival to Zumbahua. The AMS group included 141 women and 158 men of ages from 4 months to 97 years. A total of 240 patients (age average: 32.65 ± 0.08 years) were diagnosed with AMS (as NO HAPE), while 59 patients (age average: 32.3 ± 3.4 years) had HAPE. As to the altitude of residence, 238 patients lived at low altitude (< 100 m above sea level), whereas 61 patients permanently lived high altitude (> 2,700 m above sea level) including 50 patients from the Zumbahua area. The high-altitude group included 49 *indigenes* and 250 *mestizos*. Demographic and health variables were recorded for at least 80.3% of the patients. The selection bias was thus avoided.

3.2. Differences between HAPE and AMS groups

Multiple *a priori t*-tests were run to check if the split of the sample into HAPE and NO HAPE (AMS) groups was appropriate. Thus, 10 out of 12 clinical endpoints were statistically different between groups (Table 1). Breathing rate and heart rhythm in the HAPE group were higher compared to the AMS group ($t(256) = 7.78$, $p < 0.001$ and ($t(295) = 3.12$, $p < 0.01$ respectively), which provoked a profound hypoxemia. The blood O₂ saturation in the HAPE group dropped to 60%, far below the AMS group. The intolerance to high altitude made the hematocrit (49.8%) and hemoglobin (16.5 g/dL) levels in the HAPE group be higher compared to the AMS group (40.47% and 13.2 g/dL respectively). The difference in the hemoglobin levels (3.3 g/dL) was not due the unequal sex distribution, since women have mean levels of approximately 12% (1.9 g/dL) lower than men. Finally, leukocytosis (white blood cell counts $> 11 \cdot 10^9/L$) was a distinctive feature of HAPE. An information bias could definitely be ruled out.

3.3. Analysis of HAPE risk factors

HAPE prevalence and associated descriptive (risk) variables were computed by the Cramer's V test. Demographic factors like ethnicity, sex, and age, environmental factors like the altitude of residence, and antecedents of a recent stay at sea level (Table 2), as well as health status variables like systemic blood pressures, heart rhythm, and blood O₂ saturation (Table 3) were significantly associated with HAPE

susceptibility. Finally, HAPE risk was significantly associated with elevated white blood cell numbers and hemoglobin (Table 3).

Adjusted ORs for HAPE prevalence compared to AMS prevalence were obtained after a simple logistic regression. High prevalence of HAPE was characteristic of *indigenes*. In contrast, the HAPE risk was lower in females and significantly varied with age. The HAPE prevalence was significantly lower in individuals living at low altitude compared to high-altitude residents (0.014 times). Indeed, only 11 out of 59 HAPE patients permanently lived at low altitude. In *indigenes* permanently living at high altitude, a recent sea level-trip increased the odds of suffering from reentry HAPE (OR = 0.049) so that two out of three of these patients suffered from reentry HAPE. With 95 % of the individuals living at low altitude, the *mestizo* group had 76.2 more odds of having AMS ($p < 0.001$). As to vital signs, an elevation of systemic blood pressure may decrease HAPE risk. Interestingly, high hemoglobin increased the odds of having HAPE. Finally, leukocytosis was present in 33% of HAPE patients, but none of the AMS patients.

The objective of the multiple logistic regression analysis was to find an equation that best predicted the occurrence of HAPE compared to AMS as a function of its independent variables. Such an equation may provide information about their attributable fraction or *weight*. The analysis was only conducted on those significant variables that had an annotated value in at least 80% of the cases in the Cramer's V test. Demographic and environmental variables were computed separately given the complex collinearity structure that sometimes disguised the statistical relevance of these variables. The environmental variables were statistically significant for the fit model (Table 4). The likelihood of having HAPE compared to NO HAPE (AMS) was reckoned by the following equation: Predicted logit of *HAPE* = $2.642 - (5.665) \times \text{Residence altitude} - (2.15) \times \text{Sea level trip}$. The residence at low altitude and no *sea level-trip* antecedents were inversely related to the likelihood of having HAPE. Their relative influence on lowering HAPE risk was as follows: low altitude residence > no *sea level-trip* antecedents. Table 4 shows the multiple logistic regression analysis for demographic variables. The likelihood of having HAPE was estimated by the following equation: Predicted logit *HAPE* = $-0.942 + (3.094) \times \text{Ethnicity} - (1.099) \times \text{Sex} - (1.303) \times \text{Age}_{(1-14)} - (1.321) \times \text{Age}_{(15-24)} - (1.535) \times \text{Age}_{(25-65)}$. Nevertheless, given the influence of the other demographic variables, the multiple logistic regression analyses reflected the dependence of HAPE prevalence on age (Table 5). Female sex as well as age were negatively related to the likelihood of having HAPE, whereas the indigenous ethnicity was positively related. The relative influences on HAPE prevalence were as follows: indigenous ethnicity > age₍₁₋₁₄₎ $\approx$ age₍₁₅₋₂₄₎ > age₍₂₅₋₆₅₎ > female.

4. Discussion

This analysis depicted risk variables that may explain HAPE and specially the reentry HAPE, which has almost exclusively been documented in the South American Andean ridge. In the HAPE group, *indigenes* living at very high altitude outnumbered low-altitude residents. *Mestizos* residing at low altitude were largely stricken with AMS at high altitude, where *indigenes* from the highland suffer from reentry HAPE when returned to their homes after a brief (days) sojourn at lower altitude. From a logistic analysis, some factors may either increase (high hemoglobin) or reduce (female sex and high blood pressure) the risk for developing HAPE. Although the Andean-origin *indigenes* are supposedly well adapted to living at high

altitude, latent individual factors for developing HAPE remain that may shed some light on its etiopathogenesis.

Some hypotheses should be put forward to explain the influence of the above risk factors in HAPE. The finding that high-altitude *indigenous* residents had a higher risk of HAPE compared to those living in low altitudes was interesting because it does nothing but confirm that the Andeans present a worse tolerance to high altitude than the Ethiopian and Himalayan populations [19, 20]. Dwellers of this region of the Ecuadorian Andes were Panzaleo *indigenes*, an ethnicity of the Kichwa pedigree originally from the Amazonia, who presented a high prevalence of high altitude-induced erythrocytosis. The high prevalence of HAPE was largely due to a previous sojourn at sea level, which increased the odds of having HAPE, a phenomenon called reentry HAPE [34]. To this respect, our results are in agreement with the fact that reentry HAPE is more commonly seen in the South Americans because of their poorer adaptation to high altitude [24, 35]. A rapid ascent (in this case in a single day) is known to be an important risk factor in this disease [5, 34]. In addition, the reentry HAPE may also be due to change in blood volume because prolonged exposure to high altitude results in CMS [36]. In this vein, hematocrit and hemoglobin levels in native Andeans increase to physiologically adapt to high-altitude-induced hypoxemia [20, 22, 37, 38]. A chronic hypoxia of high altitude causes increased muscularization of the pulmonary arterioles, thus generating excessive pulmonary arteriole pressure on the reascent to high altitude [39]. Enhancement of blood pressure (Table 4) may compensate pulmonary vasoconstriction, while a blunted reactivity of the blood pressure to high altitude may lead to HAPE [40, 41].

Although the role of sex in the susceptibility to HAPE has been controversial [5], our results are in agreement with the fact that women were more tolerant to HAPE than men [42, 43]. The reason is that, under the influence of progesterone, women may manage alveolar ventilation and oxygenation better [44] and have less erythropoietin and hemoglobin than men [45, 46]. Multiple linear regression analyses confirmed that age has an impact in HAPE [24, 47, 48]. Vulnerability to HAPE is likely to be high in childhood, and it then decreases with aging as a result of age-dependent decline in hemoglobin levels [49]. If that was the case, the role of hemoglobin should be investigated [50].

5. Conclusion

In summary, although this study was a retrospective and single-center observational analysis. it posited the hypothesis that susceptible Andean communities like the Panzaleo *indigenes* may dramatically underestimate the adverse effects of shear forces in pulmonary artery pressure induced by the return to high altitude, which along with their probability of having a high hematocrit would increase the rate of intravascular hemolysis leading to HAPE. What causes a high haemoglobin mass in this specific Andean community may be an interesting avenue to elucidate the etiopathogenesis of HAPE.

Declarations

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DECLARATIONS

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Conflicts of interest/Competing interests

The authors declare they have no conflict of interest.

Ethics approval

Study approved by the CBH Ethics Committee.

Consent to participate

Not applicable.

Consent for publication

Consent approved by the CBH Ethics Committee.

Availability of data and material

Data will be available on reasonable request.

Code Availability

Analyses were carried out

Author's contributions

Conceptualization: Santiago Ballaz. and Anita Villafuerte. Methodology: Karen Sánchez and Wilfre Toledo. Formal analysis: Karen Sánchez. Writing–review & editing: Santiago Ballaz. Supervision: Anita Villafuerte.

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Tables

Tables 1-5 are included in the Supplementary Information section.

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