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Acute Mountain Sickness, High Altitude Pulmonary Edema, and High Altitude Cerebral Edema: A view from the High Andes

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ABSTRACT

Background: Travelling to high altitude for entertainment or work is sometimes associated with acute high altitude pathologies. In the past, scientific literature from the lowlanders' point of view was mostly based on mountain climbing. Nowadays, descent is not mandatory in populated highland cities.

Methods: We present how to diagnose and treat acute high altitude pathologies (hypobaric hypoxic diseases) based on 50 years of experience in both: high altitude physiology research and medical practice as clinicians, in La Paz, Bolivia (3,600 m; 11,811 ft), at the High Altitude Pulmonary and Pathology Institute (HAPPI – IPPA).

Results: Acute Mountain Sickness, High Altitude Pulmonary Edema, and High Altitude Cerebral Edema are medical conditions faced by some travelers. These can occasionally present after flights to high altitude cities, both in lowlanders or in high altitude residents during re-entry, having spent more than 20 days at sea level.

Conclusions: Traveling to high altitude should not be feared as it has many benefits; Acute high altitude ascent diseases can be adequately diagnosed and treated without descent.

1. Background

Planet Earth is not a smooth sphere, it has geographic spikes that include: the Himalayas [max. elevation 8,848 m; 29,029 ft], the Andes [max. elevation 6,962 m; 22,841 ft], the Alps [max. elevation 4,809 m; 15,776 ft], the Transatlantic mountains [max. elevation 4,528 m; 14,856 ft], the Rocky mountains [max. elevation 4,528 m; 14,856 ft], and several others (Sayre et al., 2018). Not all mountains are inhabitable, being the Andes among the most populated. Some high altitude destinations include Lhasa, Tibet, China (3,650 m; 11,975 ft), Cusco, Peru (3,300 m; 11,000 ft), La Paz, Bolivia (3,100 m - 4,100 m;10170 ft - 13,451 ft), Potosi, Bolivia (4,100 m;13,451 ft), etc.

Originally, Acute Mountain Sickness (AMS), High Altitude Pulmonary Edema (HAPE), and High Altitude Cerebral Edema (HACE) were described as associated with mountain climbing. Due to the alarming symptomatology, travel to high altitudes for entertainment purposes or for residence is still feared by most around the world. Particularly because classically, no apparent causes of these diseases were found other than the exposure to the hypobaric hypoxic environment. However, our experience in Bolivia, living and working in La Paz and El Alto cities, between 3,100 m and 4,100 m of altitude, with over 2.3 million inhabitants, provides us with a different point of view. High altitude should not be feared, and it should be understood in its risks and even in its benefits. It is important to note that the normal arterial partial pressure of oxygen (PaO_2) in La Paz is 60 mmHg, 1/3 less than at sea level. Under certain circumstances, upon arrival at high altitude, children and adults (newcomers or native resident re-entry) can sometimes suffer AMS, HAPE, and/or HACE.

With over 50 years of experience in high altitude medical practice, we present our perspective on "physiologic adaptation" and these three most common high altitude-related illnesses. Their prevention, treatment, and our high altitude recommendations are also detailed to ensure the well-being of all those traveling to high altitude.

1.1. *High altitude physiology*

High altitude physiology and biology follow the laws of physics and gases in lower barometric pressure (Fig. 1). Life depends on the presence of water, carbon, multiple minerals, adequate temperature, oxygen, and its end-product carbon dioxide that plays a fundamental role in high

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altitude acid-base balance (Paulev and Zubieta-Calleja, 2005).

Partial pressure of oxygen in the inspired air (PIO_2) is defined as: $PIO_2 = FiO_2$ x (PB - 47 mmHg), where Fraction of inspired oxygen (FiO_2); Barometric pressure (PB). At sea level, $PIO_2 = 0.21 \times (760 - 47) = 149$ mmHg (Dejours, 1966). The barometric pressure reduces exponentially with increasing altitude. At 3,500 m: PB = 495 mmHg, $PIO_2 =$ 94 mmHg (Zubieta-Calleja et al., 2007).

The Oxygen Transport Triad (Pneumo-dynamic pump, Hemo-dynamic pump, and hemoglobin) plays a fundamental role in high altitude physiological adaptation (Zubieta-Calleja et al., 2020). The Earth's atmosphere, mostly composed of Oxygen 20.9 % and Nitrogen 78 %, at any altitude comes in contact with the alveoli transported by the pneumo-dynamic pump that ventilates the lungs. Oxygen transfer across the alveolo-capillary membranes responds solely to diffusion (Bodil Schmidt-Nielsen, 1995). At high altitude, the differential alveolo-capillary oxygen pressure is reduced (from 5 to 2 mmHg) due to lower barometric pressure and adaptation (Cudkowicz et al., 1972). The respiratory cascade is flatter at high altitude (Peacock, 1998).

Hemoglobin plays a fundamental role in the capture and transport of oxygen, with dissolved oxygen being practically insignificant in the transport of oxygen itself, however playing the role of maintaining the oxygen saturation equilibrium in hemoglobin. The Oxygen Content in arterial blood (CaO_2) = $SaO_2 \times 1.34 \times Hb + 0.003$ (PaO_2). The hemodynamic pump (cardiovascular system) then plays the role of transporting hemoglobin with oxygen (and all other plasma constituents) from the lungs to the mitochondria in the tissues. As blood returns to the lungs, circulation transports CO_2 to the lungs for partial exhalation, maintaining adequate levels for an optimal acid-base status with a pH of 7.4. At sea level, the partial pressure of arterial oxygen (PaO_2) is around 100 mmHg, and the SaO_2 is 95–99 %. In La Paz (3,500 m), it is 60 mmHg, and SaO_2 is 88–92 % (Zubieta-Castillo and Zubieta-Calleja, 1996).

1.2. High altitude physiologic adaptation

Many authors use the term "acclimatization" to high altitude. We believe that this term's use should be referred only to climatic changes, not hypoxic altitude changes. Instead, we differentiate adaptation into two types: Genetic and Physiologic. The first takes many millions or thousands of years, whereas the latter includes short to long-term essential survival changes (Zubieta-Calleja, 2020).Symptomatic physiologic adaptation to high altitude is adequate in the great majority of the cases, within 2 or 3 days. Ventilation (pneumo-dynamic pump) and Circulation (Hemo-dynamic pump) increase upon arrival and play the initial fundamental role of physiologic adaptation. Subsequently, optimal hematologic adaptation is achieved following the High Altitude Adaptation Formula = Hemoglobin (Hb)/ time (Zubieta-Calleja et al., 2007). Arriving at a fixed altitude, coming from sea level, a logarithmic increase of hemoglobin is observed (Fig. 2). At 3,500 m, this curve takes approximately 40 days to reach the top plateau, where the final optimal adaptation is achieved (Zubieta-Calleja et al., 2007).

Initial hyperventilation upon arrival to high altitude reduces the arterial partial pressure of carbon dioxide ($PaCO_2$) (Lenfant and Sullivan, 1971; Rahn and Otis, 1948; Santolaya et al., 1989; Teppema and Berendsen, 2013). The resulting increase in pH above normal values is referred to as respiratory alkalosis. This condition brings forth inadequate metabolic function along with HIF and VEGF production, and the increase of EPO and NO. However, alkalosis cannot be sustained permanently, and the kidney eliminates bicarbonates returning pH to normal (Fig. 2). The maintenance of a normal pH is fundamental for high altitude physiological adaptation and optimal cellular function. Once pH is restored, despite being the $PaCO_2$ lower, there is no chronic respiratory alkalosis but rather an optimal adaptation that requires high altitude correction factors of the Van Slyke Formula to interpret acid - base balance (Paulev and Zubieta-Calleja, 2005).

For example, reaching the Everest summit requires an optimal pH following our acid-base high altitude correction factors (Zubieta-Calleja, 2012). SpO_2 reduces as the altitude increases following the hemoglobin oxygen dissociation curve (Fig. 3). It is important to note that when measuring SpO_2 at high altitude, there are big variations as evidenced by the breath holding test (Fig. 4) (Zubieta-Calleja and Zubieta-Castillo, 1998). Arterial blood gases at high altitudes have a lower PaO_2, a lower $PaCO_2$, and a normal pH range (Fig. 5). According to Prof. Dr. Gustavo Zubieta-Castillo Sr. (1926 – 2015), "*The organic systems of human beings and all other species tend to adapt to any environmental change and circumstance within an optimal period of time, and never tend towards regression which would inevitably lead to death*"(Zubieta-Castillo et al., 2006).

2. High altitude acute pathologies

2.1. Acute Mountain Sickness (AMS)

Few reports specify AMS incidence in childhood: 19 % in Colorado at

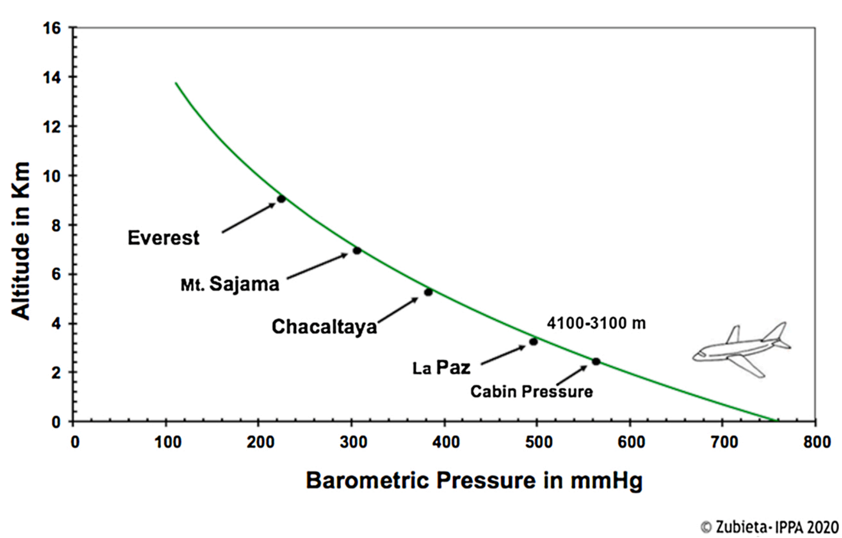

Fig. 1. Barometric Pressure – Altitude relationship showing important high altitude landmarks. The cities of La Paz and El Alto (contiguous), Mount Chacaltaya (5,270 m or 17,290 ft, IPPA's High Altitude Glass Pyramid Laboratory location). Mt. Sajama (6,542 m or 21,463 ft, highest Bolivian mountain and world highest soccer match). IPPA.

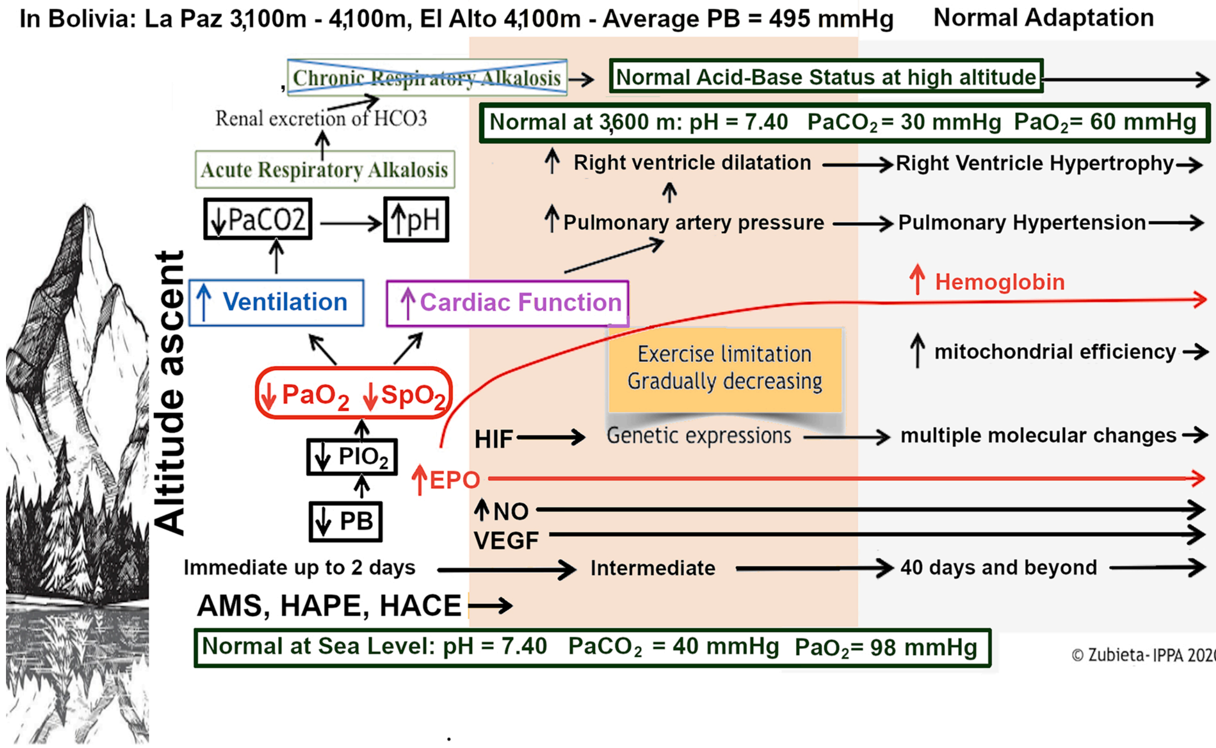

Fig. 2. Time related physiological adaptation to high altitude. Starting from the bottom left side. Red ascending line: 40 days logarithmic hemoglobin increase to reach a plateau upon arrival to 3,600 m. PB = Barometric Pressure, PIO_2=partial Pressure of Inspired Oxygen, PaO_2=arterial partial Pressure of Oxygen, SpO_2=Pulse Oximetry Saturation, $PaCO_2$=arterial partial Pressure of Carbon Dioxide, HIF=Hypoxia Inducible Factor, NO = Nitric Oxide gas, EPO = Erythropoietin, VEGF = Vascular Endothelial Growth Factor. IPPA.

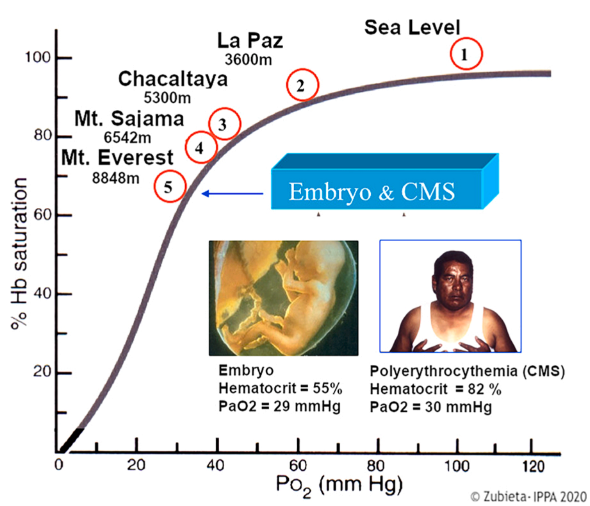

Fig. 3. Hemoglobin Dissociation curve showing different PaO_2 - SpO_2 levels in Bolivia in locations described in Fig. 1. Embryos present a PaO_2 of 29-30 mmHg (similar to those found in climbers at the summit of Mt. Everest). IPPA.

3,109 m and 34 % in Tibet at 4,550 m. Its frequency increases with the ascent rate and altitude reached. The 2001 Consensus Statement of experts concluded: "AMS is as frequent in childhood as in adulthood" (Pollard et al., 2001). It is not present below 2,000 m.

Upon arrival at a high altitude, the two pumps of the Oxygen Transport Triad are activated (Zubieta-Calleja et al., 2020). The sudden breathlessness on minimal exercise is associated with hyperventilation and tachycardia, a perfectly normal response. Nevertheless, AMS may develop within 6–24 h in some individuals.

AMS can manifest with headaches (cardinal symptom), sleeping disorders, uneasiness, dehydration from hyperventilation and diminished thirst sensation, loss of appetite, fatigue upon physical activities, and digestive gas expansion (an important factor of digestive discomfort). HAFE (High Altitude Flatus Expulsion) has been described before (Levitt et al., 1976). We propose to use HAGE (High Altitude Gas Expansion) instead, because in the city of La Paz, at 3,600 m (11,811 ft), according to Boyle's Law of Gases: due to the lower barometric pressure, maintaining the same temperature (i.e., Body temperature = 37°C), $P1 * V1 = P2 * V2$ results in 760 mmHg * 1 Lt (Gas) / 495 mmHg = 1.5. This means that the volume of gases can expand 50 % more than at sea level. The expansion of intestinal gases at high altitude gives rise to burping, flatulence, and in children could induce important digestive discomfort and vomiting due to the small size of their bodies in relation to adults.

Other significant symptoms due to their dramatic effect are nausea and vomiting that naturally produce considerable worries in parents. Actually, vomiting can often be quite alleviating for children, as the digestive process needs to save energy and oxygen for the vital organs, brain, and heart. Furthermore, it allows for a better diaphragmatic expansion, which is important for adequate ventilation. The problem with vomiting is that children can enter some dehydration that may require adequate rehydration, particularly when there is anorexia. Some present infectious superimposed diarrhea, further aggravating dehydration and malaise. Symptoms observed in preverbal children include increased fussiness, decreased appetite, poor sleep patterns, and decreased playfulness (Liptzin et al., 2018).

The diagnosis is mostly clinical, based on the fundamental fact of a recent arrival to high altitude. However, other pathologies must be discarded as high altitude should be regarded as a health / fitness test (Zubieta-Calleja and Zubieta-Castillo, 1989), and concurrent conditions that tend to aggravate the clinical picture are common (sometimes silent at sea level), e.i. viral infections (Pollard et al., 2001). Most children and

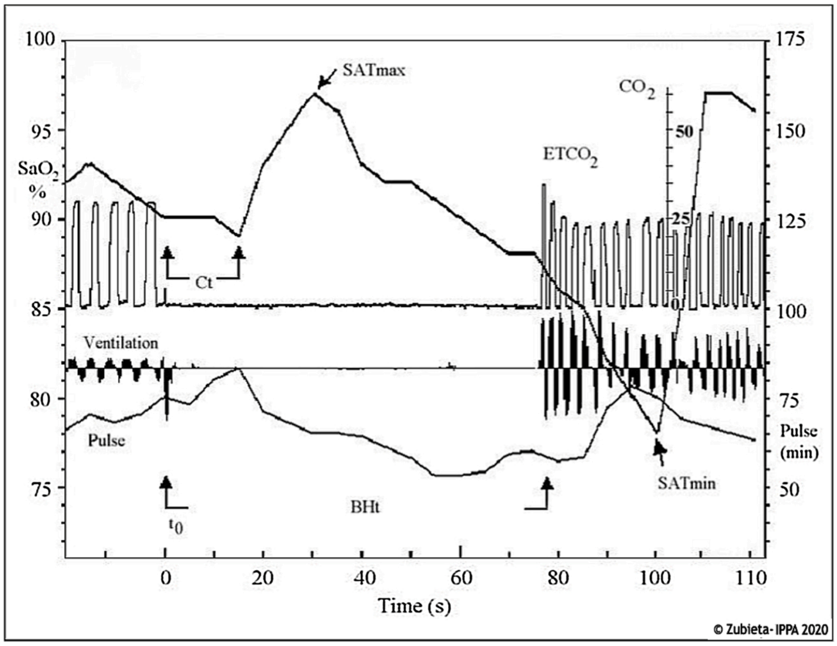

Fig. 4. Breath-holding test developed at IPPA: From top to bottom on the left: SpO_2, $ETCO_2$, Pneumotachograph Ventilation and Pulse. The black line shows SpO_2 variation during breath-holding in adults in La Paz. The resting SpO_2 (SaO_2) from pulseoximetry is 90 to 92 %. SATmax reached at 97 % (SL value) decreased to SATmin 78 % until breathing is reinstated. BHt = breath-holding time. $ETCO_2$=End-Tidal CO_2.

adults evolve favorably in 1 or 2 days.

2.1.1. Treatment

The treatment is based on the symptomatology present in each case. Mild headache can be treated with aspirin (except in children younger than 15 years of age). Acetaminophen or Ibuprofen can be used instead. If the symptoms persist, oxygen administration at 2 L/min via nasal cannula for a few hours can be helpful. Most patients evolve favorably; however, if symptoms persist, a chest X-ray and laboratory tests should be performed. We hardly ever use acetazolamide, a diuretic, and ventilatory stimulant, due to its side effects: dehydration and tingling sensation in the limbs. An additional recommendation is to use loose clothes for easy expansion of gastric and intestinal gases and the unrestricted evacuation of these. Likewise, antiflatulent medication can reduce digestive discomfort. Milk and its derivatives should be avoided or switched to lactose-free on the first day of arrival, except for breastfeeding babies. We recommend mothers to avoid eating cow's milk products, soy, wheat, corn, eggs, peanuts, cauliflower, and beans starting the day before travel and up to 2 days later after arrival to high altitude. Prophylactic medication is based on Aspirin ½ hour before the arrival to high altitude in those older than 15 years of age and Ibuprofen or Acetazolamide in those younger. Good oral hydration is essential. Upon arriving at high altitude, hyperactivity in children and adults can be a risk factor to develop acute high altitude pathologies, as shortness of breath becomes more evident under intense physical activity.

However, very few travelers may present the most feared scenarios: HAPE and very rarely HACE, both preceded by AMS, the day after arrival, and up to 3 days later.

2.2. High Altitude Pulmonary Edema (HAPE)

Among the first to describe HAPE was Charlie Houston (Houston, 1960). Overall, the incidence of HAPE in travelers to an altitude of 4,550 m was reported to be 1.5 % (Pollard et al., 2001). In general, HAPE incidence is around 1 in 10,000 visitors (Giesenhagen et al., 2019). Although the incidence is low, it is indeed a high-risk pathology that can lead to a fatal outcome if not diagnosed and treated promptly. Hence it becomes of utmost importance that pediatricians and physicians treating children and adults at high altitudes be adequately informed. This paper is beyond the scope to explain the possible causes proposed elsewhere (Imray et al., 2010; Maggiorini, 2010; Scherrer et al., 1996).

2.2.1. Risk factors

It is important to note that the rate of ascent and altitude reached is associated with a higher HAPE incidence. Commonly, it presents after 24 h but can present up to several days later (Coudert, 1985). It can also be repetitive on several entries and is termed re-entry HAPE in normal high-altitude residents returning from lower altitude travel. The time of stay at sea level is a transcendental aggravating factor. Based on our studies, in adult residents of the city of La Paz (3,100−4,100 m), it has been observed that going to sea level, there is a linear decrease in hemoglobin, hematocrit, and the number of red blood cells, lasting 20 days, complicating re-entry adaptation upon returning to high altitude (Zubieta-Calleja et al., 2007).

Consequently, it can be assumed that children going to sea level for less than a week should have a very low probability of suffering HAPE when returning to high altitude. Hematological adaptation to high altitude takes twice the length of time compared to the adaptation to sea level. It takes about forty days to build an optimal hematocrit upon arrival to the city of La Paz (Zubieta-Calleja et al., 2007). However, further studies in children need to be carried out. Aggravating factors include the altitude reached, the exertion, exposure to cold, congenital heart disease, individual susceptibility, perinatal pulmonary hypertension, and viral infections fundamentally (Zubieta-Calleja and Zubieta-Castillo, 1989). HAPE can appear in children that present some congenital heart anomaly such as Patent Ductus Arteriosus (P.D.A.), Interatrial Communication (I.A.C.), and others (Allemann et al., 2006; Gamboa and Marticorena, 1972; Penaloza et al., 1964). Comorbidities should always be discarded.

2.2.2. Diagnosis

HAPE diagnosis results from a clinical interpretation of the symptoms and signs: coughing, insomnia, cyanosis, tachycardia, tachypnea, shortness of breath at rest, marked lassitude, and incoordination. Physical examination reveals rales on chest auscultation, the "Hape tongue", bloody sputum (advanced cases), very low pulse oximetry

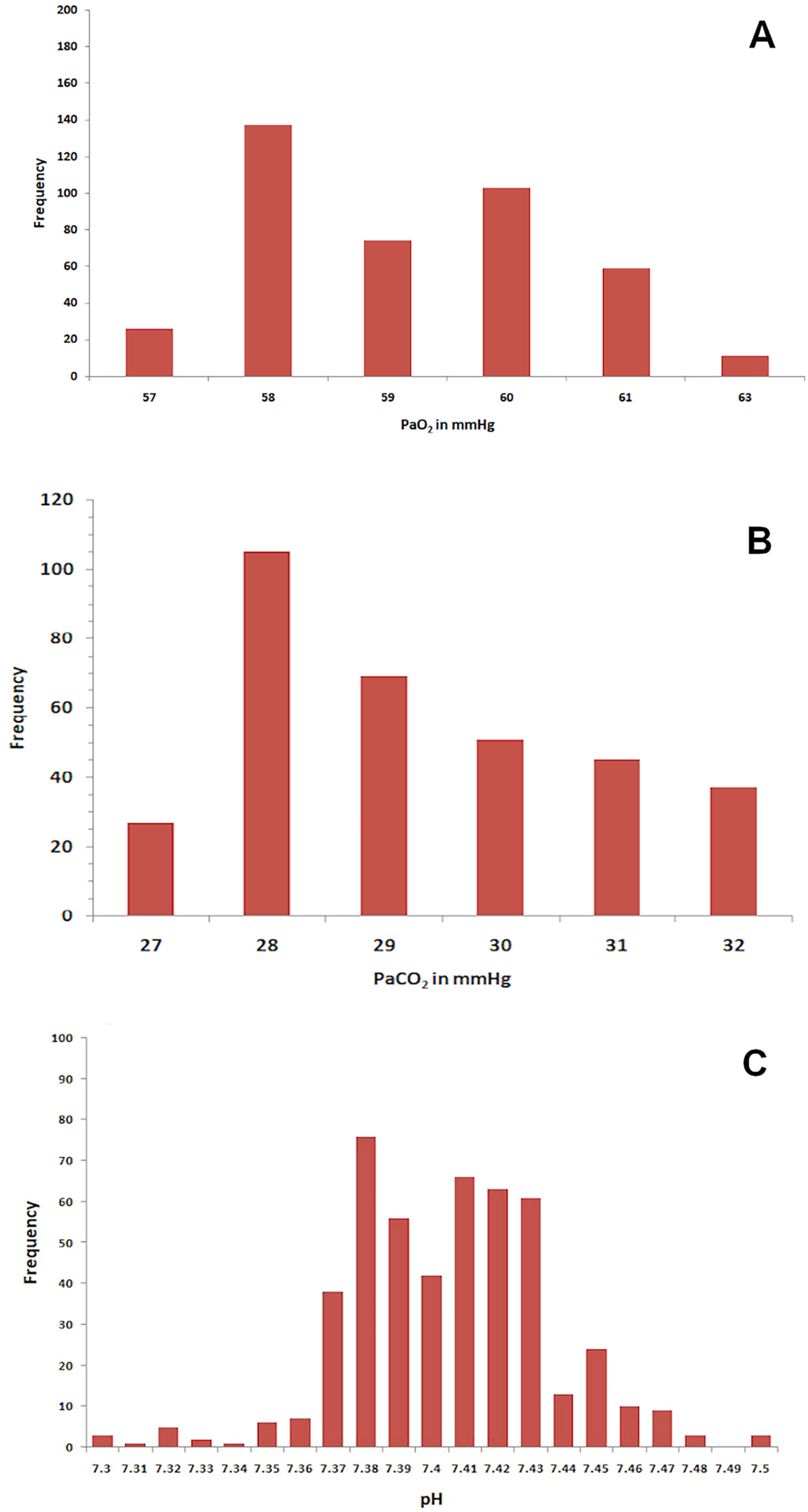

Fig. 5. Arterial Blood gas tensions in normal teenagers residing between 3,100 m and 4,100 m in La Paz. A) PaO_2 distribution n = 478; B) $PaCO_2$ distribution n = 478; C) Arterial pH distribution n = 503.

(SpO_2), and low arterial partial pressure of oxygen (PaO_2) in arterial blood gases (Zubieta-Calleja and Zubieta-Castillo, 1989). The normal values for SpO_2 in the city of La Paz are 88–92 % (Zubieta-Castillo and Zubieta-Calleja, 1996). At this altitude, children having lower values than 85 % should be closely observed and followed up. This varies according to the altitude in children (Ucrós et al., 2020). The "Hape tongue", previously described by us, is of great importance as it can aid significantly in the diagnosis, although it is not always present (Zubieta-Calleja and Zubieta-Castillo, 1989). The tongue is white, suggesting local desquamation but with irregularly distributed bright red areas

Fig. 6. HAPE tongue (local desquamation with irregularly distributed bright red areas) in 2 different children, also seen in adults. Interestingly, some COVID-19 patients can also present this type of tongues.

(Fig. 6). There seems to be a similarity of irregular presentation of the focal edema patchy infiltrates in the chest X-ray, surrounded by correctly functioning normal lung areas, sometimes present only on one side. The Chest X-ray and/or Chest CAT scan is conclusive in the diagnosis in most cases (Fig. 7). The electrocardiogram reports sinus tachycardia, usually a high pointed P-wave, a right axis deviation of QRS, and a modified T-wave reflecting right ventricular overload (Coudert, 1985). It is also advised that arterial blood gases and hemograms be performed considering each altitude's average values (Fig. 5).

2.2.3. Treatment

Most of the symptoms can be treated adequately: headaches with analgesics, and shortness of breath with bed rest in semi-fowler or fowler position. When children present HAPE when going with their parents to higher altitudes for entertainment, the best solution is to administer oxygen via nasal cannula (2-3 L/min) if tolerated or in oxygen tents, or in oxygen enriched rooms, which are much more comfortable. The oxygen is sufficient to reduce pulmonary artery pressure. Simply resting at high altitude can help resolve HAPE. This has been shown in children going to La Oroya, Peru (Marticorena et al., 1964). Although some authors advise several treatments (Liptzin et al., 2018), we do not recommend the routinary use of antibiotics, corticoids, nifedipine and/or diuretics like furosemide. They are unnecessary in most cases as they can aggravate dehydration, resulting from vomiting, hyperventilation, and anorexia. They can also irritate the gastric mucosa. It is also important to note that these patients and others suffering from AMS have a diminished thirst sensation. Consequently, adequate oral rehydration, is recommended, unless there is vomiting, where IV infusions become mandatory. The Gamow bag in the mountain has been proven useful (Freeman et al., 2004; Zafren, 1998).

2.2.4. Prognosis

Resolution of HAPE in children is quite fast between 24 and 48 h, and not so in adults where it can last much longer (Fig. 7). This implies that children can be discharged promptly without suffering the inconvenience of a lengthy hospitalization. Children going to lower altitudes will likewise evolve favorably within 24 h. However, in high altitude cities like La Paz (3,100−4,100 m), where there is adequate medical care based on know-how and advanced hospital resources, it is unnecessary to descend. Our Institute has a Hyperoxic/Hypoxic Adaptation Chamber

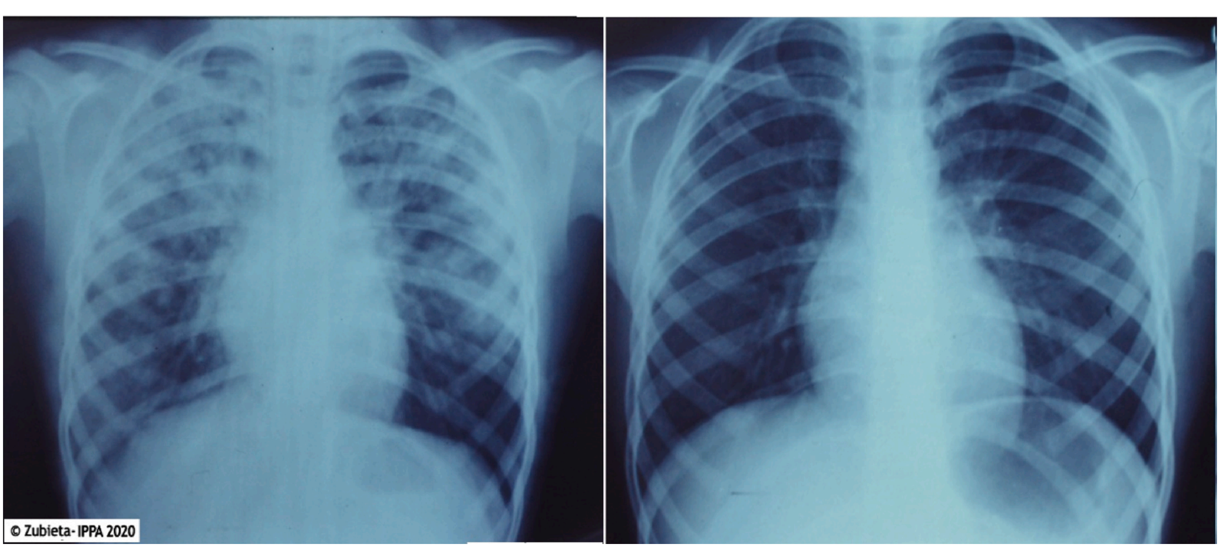

Fig. 7. A child's HAPE Chest X-Rays. Left: Irregular focal cotton-like edema areas surrounded by functioning lung areas, sometimes only one sided. Right: Recovery after a couple of days, complete clearance without sequelae.

that greatly aids in prompt recovery. HAPE resolution leaves no sequelae (Fig. 7) (Zubieta-Calleja et al., 2020). In our 50 years of practice at the High Altitude Pulmonary and Pathology Institute (HAPPI - IPPA) in La Paz, we have never had a fatal outcome resulting from any high-altitude pathology. Awareness and education of pediatricians and physicians at high altitude has reduced the negative outcomes. Better habitat conditions, adequate nutrition, long flights in pressurized airplane cabins at a comparative altitude of 2,500 m (8200 ft) also positively affect adaptation to high altitude. Short flights of less than 1 h from sea level airports can result in a higher incidence of high altitude disease.

2.3. High Altitude Cerebral Edema (HACE)

HACE presents with headache, ataxia, behavioral changes, hallucinations, confusion, altered mental status, disorientation, decreased level of consciousness, focal neurological signs, and coma, but it is quite rare (Pollard et al., 2001). Symptoms include ataxia, confusion, or altered mental status. HACE may also occur in the presence of HAPE (Jensen and Vincent, 2018; Simancas-Racines et al., 2018).

Most cases can be diagnosed clinically. Head CAT scans or MRI can be performed, as they can aid in the diagnosis. With a predilection for the splenium of the corpus callosum, white matter edema has been found in HACE; however, all reversible (Hackett et al., 1998). Due to the different clinical presentations of HACE, we suspect that edema forms in differnt parts of the brain in different individuals, and it is not always evident in imaging. Laboratory tests should be practiced routinely in search of some comorbidities that could complicate the evolution. The treatment should be carried out as soon as possible, as with all high altitude diseases. Time is the worst enemy due to the HIF, VEGF "toxic side effects". The descent is unnecessary in high altitude cities but necessary for those on the mountain. Dexamethasone can be used, 10 mg (Oral), or intramuscularly (I.M.), particularly in the mountain. The administration of oxygen should be permanent, maintaining $SpO_2 > 90$ %. Some have used the Gamow bag, a portable, manually inflated hyperbaric chamber, which has been said to be lifesaving in the mountains (Zafren, 1998). In our Institute, we utilize the Hyperoxic/Hypoxic Adaptation Chamber, which has resulted in a 100 % favorable evolution in all the cases we treated over the years.

3. Benefits of exposure to high altitude

Concerning the advantages of children going to high altitudes, it is essential to mention that those frequently suffering from asthma crisis at sea level significantly improve and can even drop their anti-asthma medication at high altitude. This has to do with lower humidity in the environment and a decrease of pollens and fungi in the inspired air. Chronic hypobaric hypoxia may decrease the incidence of asthmatic crisis, yet to be studied. At the Bogomoletz Institute in Kiev, Ukraine, hypoxia treatments in children with asthma have shown significant improvement (Serebrovskaya et al., 2003).

Fetuses in the maternal womb develop in a very hypoxic environment. In the city of La Paz, we have found that right after delivery, the umbilical cord has an average PaO_2 of around 30 mmHg (Fig. 3). Umbilical cord sampled right after a standard delivery (without clamping) at 3,500 m reports: $PaO_2 = 28$mmHg, $PaCO_2 = 29$mmHg, pH = 7.28, $PvO_2 = 19$ mmHg, $PvCO_2 = 47$mmHg, and pH = 7.12 (Zubieta-Castillo and Zubieta-Calleja, 2008). In order to measure the correct arterial oxygen levels in the newborn, it is fundamental to sample the umbilical cord vein (with oxygenated blood going to the neonate) as if it were the arterial blood gases in children. This environment, along with fetal hemoglobin, grants the human organisms a survival mechanism that is fundamental in later life. Prof. Dr. Gustavo Zubieta-Castillo Sr. (1926–2015) proposed that humanity could adapt to live in the hypoxic environments of the summit of Mount Everest 8842 m (1/3 the barometric pressure of sea level), using this observation as one of the sustaining arguments (Zubieta-Castillo et al., 2003).

The organism, facing chronic hypobaric hypoxia, can survive sea-level intolerable hypoxic levels. The COVID-19 pandemic has made it evident that previously feared extreme hypoxia can rapidly happen at sea level and is referred to as “Silent Hypoxemia”(Zubieta-Calleja and Zubieta-DeUrioste, 2020). Tolerance to hypoxia paradoxically grows as altitude increases (Zubieta-Calleja et al., 2013). This means that the higher humans go, the lower levels of hypoxia they can tolerate. This is directly related to an adequate increase of hemoglobin levels acquired over time (40 days for adults in the city of La Paz) and a lower $PaCO_2$ at high altitudes (Zubieta-Calleja et al., 2007). High levels of $PaCO_2$ at high altitude are a high-risk variable and should be managed adequately to avoid serious health hazards. The advantages of lower barometric pressure and physiological adaptation to hypobaric hypoxia can even be extended to improve future space travel (Zubieta-Calleja and Zubieta-DeUrioste, 2018; Zubieta Calleja and Zubieta-DeUrioste, 2019).

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Authors’ contributions

Both authors contributed equally.

Declaration of Competing Interest

The authors report no declarations of interest.

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