

March 2nd, 2021, La Paz – Bolivia

It is a great honor to address ourselves to you in response to the observations made by a group of sea-level self-denominated “high altitude experts” to the Chief Editor of the Respiratory Physiology and Neurobiology in relation to the article “**Acute Mountain Sickness, High Altitude Pulmonary Edema, and High Altitude Cerebral Edema: A view from the High Andes**” by Prof. Dr. Gustavo Zubieta-Calleja and Dr. Natalia Zubieta-DeUrioste, asking for a retraction:

The observations were:

1. There is no evidence that “adaptation” is a cause of the “reduction of the differential alveolo-capillary oxygen pressure”. This is the result of the biochemistry of hemoglobin and the fact that gas exchange in the lung is occurring over a steeper portion of the hemoglobin O₂ dissociation curve, such that for the same degree of venous admixture the alveolar-arterial difference is lower at high altitude.

Response 1:

This article is based on our perspective. When we say a view from the High Andes, it is our opinion. We believe adaptation is the process of adjusting to circumstances, making life possible, and we mean “physiological adaptation”. We are aware others have defined “adaptation” only as a process solely associated with genetic adjustments. Nevertheless, we disagree with this definition since we live and work at high altitude, and we don’t agree with the idea of high altitude representing a threat over time. Multiple diseases are not clearly understood at high altitude thus far, as we see it.

We include several citations backing up these arguments. At high altitude, the differential alveolo-capillary oxygen pressure is without a doubt reduced (from 5 to 2 mmHg) due to lower barometric pressure, and it is a process of adaptation (Cudkowicz et al., 1972). The respiratory cascade is flatter at high altitude, which is also adaptation (Peacock, 1998). At a higher altitude, at 5,230 m, in Chacaltaya, the Bolivian Aymara natives present an A-aPO₂ of 1 ± 1.4 mmHg (Lundby et al., 2004). A lower level of ventilation/perfusion mismatch is presumed (Lundby et al., 2004), and a 173% higher diffusion capacity in the Bolivian Aymara was observed (Wagner et al., 2002).

Lundby, C., Calbet, J.A.L., Van Hall, G., Saltin, B., Sander, M., 2004. Pulmonary gas exchange at maximal exercise in Danish lowlanders during 8 wk of acclimatization to 4,100 m and in high-altitude Aymara natives. *Am. J. Physiol. - Regul. Integr. Comp. Physiol.*
<https://doi.org/10.1152/ajpregu.00725.2003>

Wagner, P.D., Araoz, M., Boushel, R., Calbet, J.A.L., Jessen, B., Rådegran, G., Spielvogel, H., Søndegaard, H., Wagner, H., Saltin, B., 2002. Pulmonary gas exchange and acid-base state at 5,260 m in high-altitude Bolivians and acclimatized lowlanders. *J. Appl. Physiol.*
<https://doi.org/10.1152/japplphysiol.00093.2001>

2. The equation giving the content of dissolved oxygen should be $0.003 \times \text{PaO}_2$
 $(\text{CaO}_2) = \text{SaO}_2 \times 1.34 \times \text{Hb} + 0.003 (\text{PaO}_2)$.

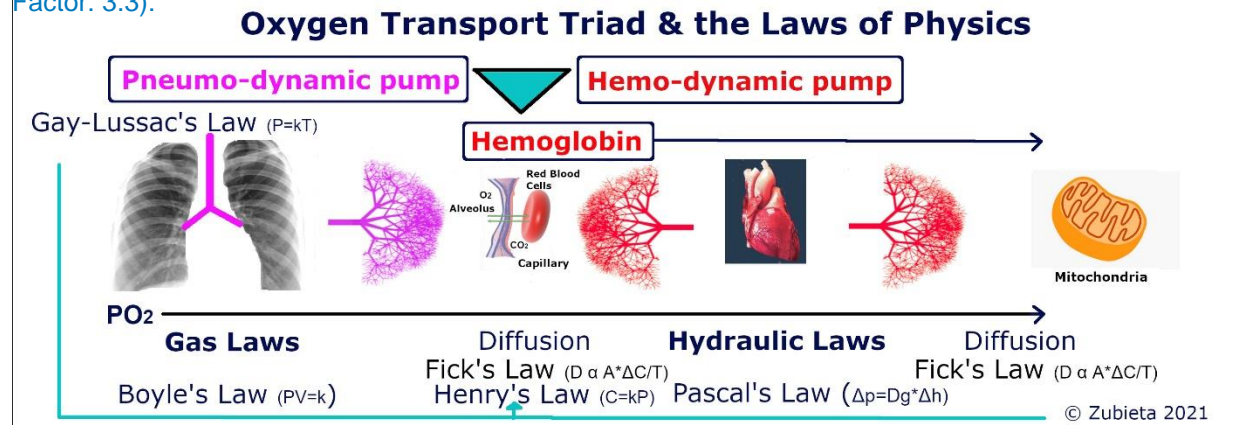
Response 2:

Perhaps it would look better, but what we wrote is mathematically correct and would need no rectification. In math, brackets mean the multiplication of the value within the brackets with the number outside the brackets. However, we have modified it in our [new paper](#).

3. The cardiovascular system does not transport hemoglobin and oxygen to the mitochondria. Rather, it transports them to the capillaries and then a diffusion process is necessary for O₂ to reach the mitochondria. This tissue diffusion process should be mentioned.

Response 3:

We are well aware of this technical wording issue. We were more interested in the concept of oxygen being carried from the atmosphere to the mitochondria. But we have reworded it to avoid confusion. It is now published (by invitation) in the International Journal of Environmental Research and Public Health (Impact Factor: 3.3):



4. The term « High Altitude Physiologic adaptation » is incorrect. Instead, the term “acclimatization” is widely used by the scientific community to refer to transient physiological readjustments while “adaptation” must be limited to genetically transmissible changes because they are integrated into the gene pool of a particular population or species.

Response 4:

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)

Other authors seem to agree with us. They talk about “physiological models of adaptation” and acclimatization:

Little MA, Thomas RB, Garruto RM. A half century of high-altitude studies in anthropology: introduction to the plenary session. *Am J Hum Biol.* 2013 Mar-Apr;25(2):148-50. doi: 10.1002/ajhb.22356. Epub 2013 Feb 5. PMID: 23382069

Frisancho uses the term “functional adaptation” 40 times in this paper:

A. Roberto Frisancho, Developmental Functional Adaptation to High Altitude: Review
First published: 22 February 2013 <https://doi.org/10.1002/ajhb.22367>

One of the authors who wrote a question, even cited Frisancho’s paper in:

Childebayeva A, Goodrich JM, Leon-Velarde F, et al. Genome-Wide Epigenetic Signatures of Adaptive Developmental Plasticity in the Andes. *Genome Biol Evol.* 2021;13(2):evaa239. doi:10.1093/gbe/evaa239, recently published. They even used the term “adaptive developmental plasticity”, that supports a physiological process.

And, Storz & Scott also talk about Physiological adaptation:

Storz JF, Scott GR. Life Ascending: Mechanism and Process in Physiological Adaptation to High-Altitude Hypoxia. *Annu Rev Ecol Evol Syst.* 2019 Nov;50:503-526. doi: 10.1146/annurev-ecolsys-110218-025014. Epub 2019 Sep 3. PMID: 33033467; PMCID: PMC7540626.

One possible mean by which the environment can influence individual traits is through epigenetic modifications that change the expression of DNA ([Frisancho 2009](#); [Szyf and Bick 2013](#); [Maccari et al. 2014](#); [Julian 2017](#); [Childebayeva et al. 2019](#)).

We think that Physiological Adaptation, includes epigenetic modifications or rather expressions. There is no reason to reject this concept.

Finally, as scientists, we have the right to propose new things: As an example, Luc. Teppema proposed: “In the view of this author, it is confusing to state that the only CNS contribution to the isocapnic HVR is depression of ventilation (Funk & Gourine, [2018](#)). The term decline may be preferred over depression (hypoxic ventilatory decline; HVD; Teppema & Dahan, [2010](#)).”
What is wrong with Luc defining the new term?

Teppema, L.J., Smith, C.A., 2013. Rebuttal from Luc J. Teppema and Curtis A. Smith. J. *Physiol.* <https://doi.org/10.1113/jphysiol.2013.259879>

5. The so-called “High Altitude Adaptation Formula” is not clearly defined and the reference is not properly quoted. It is not accepted by the scientific community.

Response 5:

The High Altitude Adaptation Formula is now clearly defined in the text:
High Altitude Adaptation Formula = Hemoglobin / time (Zubieta-Calleja et al., 2007).

Zubieta-Calleja, G.R., Paulev, P.E., Zubieta-Calleja, L., Zubieta-Castillo, G., 2007. Altitude adaptation through hematocrit changes. *J. Physiol. Pharmacol.* 58 (5(Pt 2)), 811–818.

This paper is in Pubmed, and if you check google Scholar, it has 73 citations. We have also been personally asked for permission to use the graph and data in some publications. Several scientists have even told us that it is “a classic”, more than once. The sentence we coined, “Full hematological adaptation to high altitude is achieved when the increase of red blood cells reaches a plateau and stops”, can be found in multiple publications. Even 2 books written by scientists have used these concepts as part of the “classic” literature.

Single Best Answer MCQs in Anaesthesia: Volume II Basic Sciences

By Cyprian Mendonca,, Mahesh Chaudhari,, A Pitchiah

Physiology of Exercise

By Dr. Shyam Lal Koley

So, we believe it is well recognized in the scientific literature.

6. The authors suggest that respiratory alkalosis or low PaCO₂ would be responsible for HIF and VEGF production... This is an enormous mistake. There are no data to support a stimulatory effect of alkalosis on HIF and VEGF metabolism. In fact, intracellular acidosis has been shown to stimulate HIF production. It is well established that hypoxia induces HIF production (by definition) and therefore VEGF and EPO production.

Response 6:

Yes, again, this is a wording issue. We all know “hypoxia” induces HIF, VEGF and EPO production. We agree that this could have been worded more appropriately. It is now corrected.

7. The assumption that pH goes back to normal with acclimatization is erroneous: pH never goes back to normal, especially at extreme altitudes, as renal compensation for respiratory alkalosis is never complete.

Response 7:

We must STRONGLY disagree. pH goes back to normal values in the high-altitude cities all over the world. It is possible that at extreme altitudes, there has never been “full physiologic adaptation” as time used for the studies at high altitude was insufficient, and there are other factors related to hemoglobin. In other words, the “High Altitude Adaptation Formula” was not used in those studies. It has to be clearly understood that life cannot exist without an optimal pH. This is a very basic and fundamental point of metabolism. How can they affirm that all the high-altitude residents have an abnormal pH?

We should add, that we avoided citing more of our papers (available at Pubmed), such as:

Zubieta-Calleja G, Zubieta-Castillo G, Zubieta-Calleja L, Ardaya-Zubieta G, Paulev PE. Do over 200 million healthy altitude residents really suffer from chronic Acid-base disorders?. *Indian J Clin Biochem.* 2011;26(1):62-65. doi:10.1007/s12291-010-0088-9

But we did include:

Zubieta-Calleja Jr., G., 2012. Extremely high altitude hypoxic conditions during Mount Everest expeditions, residence at South Pole stations, in Tibet and among the Andes: Van Slyke equation modification is crucially important for acid–base measurements. *J. Biol. Phys. Chem.* 12, 103–112. <https://doi.org/10.4024/17ca12i.jbpc.12.03>.

We show they used the **sea level** acid-base Van Slyke formula in measurements at 8400m on Mt. Everest and interpreted a great Acid-Base imbalance with a BE = - 7. With Gustavo's correction formulas, we showed that BE was close to 0, a normal acid-base status that allows climbers to reach the summit of Mt. Everest. In our paper we refer to “BE” as “THID” (Titratable Hydrogen Ion Difference), based on the term generated by the father of Acid-Base Status the Dane Ole Siggaard-Andersen.

And we already cited a paper that they simply don't understand!! :

Paulev, P.E., Zubieta-Calleja, G.R., 2005. Essentials in the diagnosis of acid-base disorders and their high altitude application. *J. Physiol. Pharmacol.* 56, 155–170.

We are now obliged to include 2 other papers based on our work that confirm how crucial our THID (or BE) concept is at high altitude:

Lasso Apráez, MD., J.I., 2014. Interpretación de los gases arteriales en Bogotá (2.640 msnm) basada en el nomograma de Siggaard-Andersen. Una propuesta para facilitar y unificar la lectura. *Rev. Colomb. Neumol.*

Grogono, A.W., Solarte, I., 2020. Correcting Acid Base Interpretation for High Altitudes. *Anesthesiology.*

8. The introduction of unpublished data about “breath holding” is awkward and irrelevant to the rest of the text. The corresponding reference is an abstract and no peer-reviewed paper has ever been published on this topic.

Response 8:

Zubieta-Calleja, G., Zubieta-Castillo, G., 1998. Changes in oximetry during breath holding in Normal residents of High altitude (3510m). In: Ohno, H., Kobayashi, T., Shigeru, M., Nakashima, M. (Eds.), Progress in Mountain Medicine and High Altitude Physiology, pp. 343–348. Press Committee of the 3rd World Congress on Mountain Medicine and High Altitude Physiology.

That is a reference on the full paper. It is not abstract. It was peer-reviewed by the Japanese who organized the 3rd World Congress on High Altitude Medicine and Physiology. But we also have peer-reviewed publication that we now include:

Zubieta-Calleja, G.R., Zubieta-Castillo, G., Paulev, P.E., Zubieta-Calleja, L., 2005. Non-invasive measurement of circulation time using pulse oximetry during breath-holding in chronic hypoxia. J. Physiol. Pharmacol. 56, 251–256.

It is not irrelevant and quite the opposite, extremely important to note that when measuring SpO₂ at high altitude, there are big variations that are clearly not taken into account. If proper data is not used in published papers, questionable conclusions can arise from them. These variations were already described in the cited reference: (Zubieta-Calleja and Zubieta-Castillo, 1998).

One of the fundamental measurements in high-altitude medicine is pulseoximetry. If breathing changes since SpO₂ at high altitude is in the hemoglobin oxygen dissociation curve slope, then variations of breathing make very big changes in the pulseoximeter. This is why it is important to show those variations with breath-holding.

9. The sentence by Dr Zubieta-Castillo «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» is not based on published data but purely speculative. The authors totally ignore an entire category of high altitude-related diseases in the high Andean population, namely Chronic Mountain Sickness or Monge's disease. This disease is characterized by a severe polycythemia with extremely high values of hematocrit, relative hypoventilation and worse oxygenation, right heart failure, pulmonary hypertension, and thrombotic complications. Its incidence in La Paz (El Alto) is more than 10 % of the population. This disease was first described by the Peruvian pioneer Carlos Monge and his son and thereafter studied in a great number of publications in peer-reviewed journals by leading South American scientists such as Pr. León-Velarde) as well as in China. Therefore, the author clearly overlook that there is some definite vital risk of permanent living at high altitude, as between 5 to 15% of the high Andean population suffer from Monge's disease, a "disadaptation" to high altitude conditions.

Response 9:

"Disadaptation," interesting new terminology, and purely speculative. A Peruvian PhD obviously wrote this question, systematically blocking everything we do, and permanently discrediting us within the international community because we strongly disagree with her negative view of high altitude.

She usually used "Loss of Adaptation", or Maladaptation, and even wrote a book entitled "Loss of Adaptation". Why is she allowed to change the terminology she uses?

CMS, or rather Polyerythrocythemia, are multiple diseases. We wrote several papers about it that are systematically ignored and never cited. It becomes a conflict of interest for others to cite something that goes against what they wrote. CMS is another syndrome that the lowland "high altitude experts" clearly do not understand" as the great majority have never treated one patient. Unfortunately, when they obtain data to write their papers, they do not know how to make a proper differential diagnosis.

As opposed to them, we believe in life plasticity and physiologic adaptation, as Frisancho, and as more and more data around the world confirm the constant adaptative changes associated with different stimuli. This is a comment purely based on a conflict of interest.

The citation by Dr. Zubieta-Castillo, was published many times. It is a postulation based on several arguments on over 40 years of research, living, and successful treatments at high altitude. The Adaptation Formula was based on this affirmation.

10. The whole paragraph about HAFE (High Altitude Flatus Expulsion) or HAGE (High Altitude Gas Expansion) is based on anecdotal observations and is not recognized as an essential manifestation of high altitude related diseases. Furthermore, HAFE and HAGE are only transient phenomena related to acute pressure changes when one moves from a low to higher altitude. Once at a stable altitude, the differential pressure between the atmosphere and GI tract disappears.

Response 10:

Joseph Hamel, a scientist from Geneva, was the first to describe the syndrome of high altitude flatus expulsion (HAFE). HAFE was also mentioned by the notable Paul Auerbach, the respected president of Wilderness and Environmental Medicine, and is obtained from a citation:

Auerbach P, Miller YE. High Altitude Flatus Expulsion (HAFE). *West J Med*. 1981;134(2):173-174. PMID: PMC1272559 PMID: [18748805](#)

We proposed, (just as Paul Auerbach had done) a new term HAGE (High Altitude Gas Expansion). This is based on the fundamental Boyle's law of gases and pressures. Can we refute Boyle's law? We also calculate the expansion of gases in the abdomen. This is very important!!! It was even mentioned in an article on "the High Andes",

National Geographic Magazine April 1987, Volume 171 No. 4, by Loren McIntyre, where Gustavo Sr. and Jr. were interviewed, and it is referred to as "breaking the wind".

"Unfortunately, these experts have not yet become aware of the extreme discomfort this produces in patients, and particularly in children with their small body mass".

Their expression: "Once at a stable altitude, the differential pressure between the atmosphere and GI tract disappears" is only real in non-organic things such as bottles or balloons. And what they affirm in this observation about these being only transient phenomena is not valid. The ideal gas law $PV=nRT$ stands for any altitude. Metabolic gas output from GI digestive chemical reactions has to be the same at any altitude; however, the flatulence gas volume grows and is bigger at high altitude permanently due to the lower pressure.

The ideal gas law $PV=nRT$ stands for any altitude [38]. Metabolic gas output from GI digestive chemical reactions should be the same at any altitude. However, due to the lower pressure, the flatulence gas volume should grow and be larger at high altitude, if the same volume were to be permanently produced. Among the observations to our article, one stated, "once at a stable altitude, the differential pressure between the atmosphere and GI tract disappears", but this mainly applies to non-organic containers such as bottles or balloons.

The high-altitude flatulence was also mentioned in an article on "the High Andes", National Geographic Magazine April 1987, Volume 171 No. 4, where Loren McIntyre interviewed Gustavo Sr. and Jr., referring to it as "breaking the wind".

Furthermore, it is essential to note that gases' distension upon arriving at high altitude is not a transient phenomenon. The ideal gas law $PV=nRT$ stands for any altitude. Metabolic gas output from GI digestive chemical reactions has to be the same at any altitude. However, due to the lower barometric pressure, the flatulence gas volume grows and is more prominent at high altitude permanently. Some believe that "once at a stable altitude, the differential pressure between the atmosphere and GI tract disappears," but this is incorrect as it only applies to non-organic things such as bottles or balloons. Biology is linked to the pressure laws of physics at any altitude. This concept could help explain what Frisncho has described as the Dolicomegacolon (a loop of intestine twists around itself and the mesentery that supports it, resulting in a bowel obstruction – often a medical-surgical emergency) quite common in high altitude natives residing at 3,800m or above [39,40].

11. The hypothesis that “vomiting is an adaptive process in order to save energy and oxygen for the vital organs” is entirely non-sensical and unsupported by any controlled study.

Response 11:

This paper is about our experience with high altitude diseases, and through all these years, we have observed that after the children vomit, they feel much better. Digestion consumes oxygen and since oxygen is low due to the diminished pressures, the organism expels the extra food. To give anti-vomiting medication initially is an absolute mistake in these cases.

It could be replaced by: initial vomiting can be a relief for children. This is not the same as continuous vomiting.

12. The assumptions about acetazolamide are not correct. When properly administered at a low dose of 125mg bid, the diuretic and “tingling” effects of this drug are limited. This drug is officially recommended by scientific medical experts and governmental agencies such as the US Food and Drug Administration and the European Medicines Agency, when progressive natural acclimatization is not possible such as when arriving directly by plane from sea level to La Paz airport (4,050 m). Its benefits have been studied in a great number of double-blinded placebo-controlled trials.

Response 12:

Yes, there are many studies, but we have attended many people suffering from “tingling”, dehydration, and other causes, and we have been successful without its use. That is our unrefutable personal experience.

13. Prophylactic use of aspirin and, moreover, ibuprofen is widely debated in the scientific community, especially in children.

Response 13:

We clearly specified in the paper: “Mild headache can be treated with aspirin, except in children younger than 15 years of age”. Aspirin is used prophylactically in other diseases as well, such as coronary artery disease. The references are included in the text.

14. The statement that « HAPE is preceded by AMS » is false: HAPE can happen without being preceded by AMS symptoms.

Response 14:

That is debatable. The symptoms of AMS are: sleeping disorders, uneasiness, dehydration from hyperventilation and diminished thirst sensation, loss of appetite, fatigue upon physical activities. All these symptoms are also present in HAPE. HAPE can be preceded by AMS.

15. The assumption that “...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” is not based on any published data.

Response 15:

Unfortunately wrong. There is published data from a long time ago and by a great scientist: Hultgren. He observed that the time of sea-level stay was 10 to 14 days for re-entry HAPE to appear (Hultgren, 1996). Children from Colorado have been found to present re-entry-HAPE even after less than a week's stay at sea level (Scoggin et al., 1977). Re-entry HAPE in children that have gone to sea level generally involves long periods.

Hultgren, H.N., 1996. High-altitude pulmonary edema: Current concepts. *Annu. Rev. Med.*
<https://doi.org/10.1146/annurev.med.47.1.267>

Scoggin, C.H., Hyers, T.M., Reeves, J.T., Grover, R.F., 1977. High-Altitude Pulmonary Edema in the Children and Young Adults of Leadville, Colorado. *N. Engl. J. Med.* 297, 1269–1272.
<https://doi.org/10.1056/nejm197712082972309>

16. The “HAPE tongue” is a speculative assumption and has never been published in a peer-review journal: there is no proof that it is specific for HAPE. It can be found in many other pathological conditions, particularly in children.

Response 16:

Yes, it can be found in many other pathological conditions like COVID, a viral disease. Incidentally, we have mentioned that a viral presence in HAPE can be due to viral diseases as published in:

Pollard, A.J., Durmowicz, A., Durrer, B., Eldridge, M., Hackett, P., Jean, D., Kriemler, S., Litch, J.A., Murdoch, D., Nickol, A., Richalet, J.P., Niermeyer, S., Roach, R., Shlim, D.R., Wiget, U., Yaron, M., Zubieta-Castillo, S., Zubieta-Calleja, Barry, P., B'artsch, P., Berghold, F., Bishop, R.A., Clarke, C., Dhillon, S., Dietz, T.E., 2001. Children at high altitude: an international consensus statement by an ad hoc committee of the International Society for Mountain Medicine, 2001 High Alt. Med. Biol. (March).
<https://doi.org/10.1089/15270290152608561>.

This is not intended to be taken as a pathognomonic sign, but it can be of great help in the diagnosis specially in the mountain. Frequently, in medicine, you hardly ever find all signs described in literature at the same time.

17. It is incorrect and, in fact, dangerous to say that bed rest is sufficient to treat shortness of breath, especially when HAPE is suspected. The entire paragraph about HAPE treatment is very problematic because it does not conform to the main recommendations proposed by expert international societies such as the International Society for Mountain Medicine or the Medical Committee of the UIAA (International Union of Alpinists) or the Wilderness Medical Society. The use of glucocorticoids, nifedipine or other calcium blockers, sildenafil or other PDE5 inhibitors is clearly defined in guidelines published by these international groups and the information given here is totally misleading and may induce confusion and mistrust among the public.

Response 17:

What we present in this paper is based on our experience. We are highly successful in our treatments. We have saved many lives and international insurances from expending hundreds of thousands of dollars to evacuate patients.

Rest is fundamental, yet we have never treated the patients solely with rest, although Marticorena and Hultgren wrote and published about the proven efficacy of rest. Oxygen is basic and extremely important as it is the essential physiological pulmonary circulation vasodilator. We have had success following our methods. And this is a paper explaining our experience.

Marticorena, E., Hultgren, H.N., 1979. Evaluation of therapeutic methods in high altitude pulmonary edema. *Am. J. Cardiol.* [https://doi.org/10.1016/S0002-9149\(79\)80020-X](https://doi.org/10.1016/S0002-9149(79)80020-X)

18. The claim by the authors that they “...have never had a fatal outcome resulting from any high-altitude pathology...” is astonishing since the death toll resulting from HAPE and/or HACE is around 40% in untreated patients and many cases of death following HAPE or HACE (although the rate seems to be decreasing with greater dissemination of information to

the general traveling public) have been reported in all parts of the world, including Bolivia.

Response 18:

This is genuinely a conflicting point, although astonishingly, it is true. There has never been a casualty at our Institute, as they come to receive treatment, following the advice we provide in this manuscript. There is no way they could find any proof of someone passing away at IPPA. Because it simply has not happened. Either they are obviously not managing their HAPE patients properly, or something very strange is going on. Yes, we are aware that there have been deaths due to HAPE in the city of La Paz, but not under our care. NEVER!! We are not talking about untreated patients, as we treat all our patients.

19. The assumption that “HIF, VEGF toxic effects” would be the “worst enemy”... is just unbelievable to be read in a scientific paper. HIF is critically fundamental to much of acclimatization processes to high altitude hypoxia, a role clearly supported by the fact that the individuals who discovered and studied its effects were rewarded the Nobel Prize for Medicine in 2019.

Response 19:

HIF is indeed a magnificent discovery by Semenza and the other two awardees and is fundamental on exposure to hypoxia.

However, as with most mechanisms in physiology, it depends on the dosage. And, in some cases, HIF has also been associated with side effects, “In contrast to the acute protective roles of HIF, chronic HIF stabilization has shown to have detrimental effects. HIF1A transgenic mice develop spontaneous cardiac hypertrophy with age”. Published in:

Lee, J.W., Ko, J., Ju, C. *et al.* Hypoxia signaling in human diseases and therapeutic targets. *Exp Mol Med* **51**, 1–13 (2019). <https://doi.org/10.1038/s12276-019-0235-1>

And

Wang, L., Jin, Z., Wang, J. *et al.* Detrimental effect of Hypoxia-inducible factor-1 α -induced autophagy on multiterritory perforator flap survival in rats. *Sci Rep* **7**, 11791 (2017). <https://doi.org/10.1038/s41598-017-12034-x>

These side effects have also been described by Semenza himself:

Prabhakar, N.R., Semenza, G.L., 2012. Adaptive and maladaptive cardiorespiratory responses to continuous and intermittent hypoxia mediated by hypoxia-inducible factors 1 and 2. *Physiol. Rev.* <https://doi.org/10.1152/physrev.00030.2011>

20. The authors fail to mention that the beneficial effects of altitude for asthmatic patients are also due to increase in adrenergic activation and secretion of endogenous corticosteroids that are bronchodilating and anti-inflammatory.

Response 20:

We agree. We have not described all mechanisms involved, as it is not the focus of the paper. Interesting point. And further proof that life at high altitude is beneficial.

21. The assumption that one could permanently adapt to life at the summit of Mount Everest is utter nonsense and contrary to all clinical and physiological measurements that have been made at these extreme altitudes and documented in the peer-reviewed published literature. No study sustains this hypothesis. All studies have shown progressive physiological deterioration occurs over time above 6,000 m.

Response 21:

Unfortunately, they have not read our papers. Babies in the maternal womb have a PaO₂ of 30 mmHg similar to that at the summit of Mt. Everest. They live at the hypoxic levels of Mt. Everest. Furthermore, **Chronic Mountain Sickness patients during the Triple Hypoxia Syndrome** have a PaO₂ of 30 mmHg or lower. They are, in reality, living at the hypoxic levels of the summit of Mt. Everest. According to our Tolerance to Hypoxia formula, a subject on the summit of Mt. Everest tolerates 7 times more hypoxia than a sea-level resident. The limiting factors on the summit of Mt. Everest are cold, fatigue, lack of sleep, and malnutrition. These factors naturally bring forth progressive physiological deterioration, but they only attribute it to hypoxia, a totally blind scientific approach.

All those signing the letter to the editor about our paper, have “lived” in the mother’s uterus at the hypoxic levels of the summit of Mt. Everest. Unfortunately, the weather conditions on the Summit of Mt. Everest are extremely limiting to perform long-term studies. The conditions in those studies that describe a deterioration over time are insufficient as they do not take the time to adapt physiologically.

For a long time in history, nobody could conquer the summit of Mt. Everest. Several international expeditions failed. It was believed to be impossible. On May 29, 1953, Hillary and Sherpa mountaineer Tenzing Norgay became the first climbers confirmed to have reached the summit of Mount Everest; hence he became Sir Edmund Hillary. High altitude Guinness records are constantly being broken. We are firm believers that there will be no question about men/women adapting to the extreme levels of hypoxia, provided physiological adaptation is fully understood (which unfortunately is not). Time will tell.

22. The paragraph suggesting that high altitude natives would be protected against COVID-19 is inadequate and dangerous. The speculative articles that have suggested this hypothesis are plagued by numerous uncertainties in the data emerging in a very fluid pandemic situation. In the worst phases of the pandemic in 2020, Peru and Bolivia have been some of the most affected countries and there is no biological or clinical argument to support this “protection”.

Response 22:

As of Feb 27th, 2021:

#	Country, Other	Total Cases	New Cases	Total Deaths	Total Recovered	Deaths/ 1M pop	Tests/ 1M pop	Population
1	Gibraltar	4,235	+1	92	4,119	2,731	5,472,895	33,684
2	San Marino	3,621	+35	73	3,201	2,148	1,217,935	33,978
3	Belgium	760,809	+3,113	21,988	51,946	1,892	799,572	11,622,651
4	Czechia	1,198,168	+13,657	19,835	1,046,575	1,850	724,937	10,722,006
5	Slovenia	187,005		3,802	171,905	1,829	430,795	2,079,125
6	UK	4,154,562	+9,985	122,070	2,727,466	1,792	1,297,531	68,119,415
7	Italy	2,868,435	+19,886	96,974	2,375,318	1,605	650,913	60,403,451
8	Portugal	801,746	+1,160	16,185	711,713	1,590	799,561	10,177,175
9	Montenegro	74,183	+571	987	64,737	1,571	437,918	628,118
10	USA	29,049,946	+75,061	520,707	19,433,769	1,567	1,066,132	332,272,677
11	Bosnia and Herzegovina	130,510	+757	5,062	114,995	1,549	201,540	3,267,391
12	Hungary	414,514	+4,385	14,672	315,781	1,521	370,975	9,644,237
13	North Macedonia	101,214	+582	3,111	90,685	1,493	246,094	2,083,318
14	Spain	3,180,212	+9,568	68,813	2,617,239	1,471	823,055	46,766,659

#	Country, Other	Total Cases	New Cases	Total Deaths	Total Recovered	Deaths/ 1M pop	Tests/ 1M pop	Population
15	Bulgaria	243,946	+1,822	10,079	202,694	1,458	237,282	6,914,009
16	Andorra	10,799	+24	110	10,356	1,422	2,502,974	77,346
17	Liechtenstein	2,558	+5	54	2,484	1,414	716,073	38,200
18	Mexico	2,060,908	+8,642	182,815	1,614,614	1,408	41,234	129,817,023
19	Peru	1,308,722	+7,923	45,903	1,210,749	1,380	223,474	33,271,135
20	Croatia	241,592	+544	5,489	233,170	1,343	324,748	4,088,610
21	Panama	339,383	+682	5,810	324,156	1,333	432,600	4,358,982
22	France	3,686,813	+25,403	85,582	254,868	1,309	793,255	65,368,185
23	Sweden	652,465		12,798	N/A	1,262	583,543	10,140,462
24	Slovakia	300,775	+2,438	6,859	255,300	1,256	368,027	5,461,377
25	Lithuania	196,047	+538	3,209	181,809	1,190	777,902	2,697,214
26	Brazil	10,393,886	+67,878	251,661	9,323,696	1,178	133,928	213,547,458
27	Colombia	2,241,225	+3,683	59,396	2,138,193	1,159	221,377	51,236,893
28	Switzerland	553,867	+1,169	9,954	505,666	1,145	574,458	8,696,005
29	Argentina	2,093,645	+8,234	51,795	1,886,732	1,139	161,049	45,466,686
30	Poland	1,673,252	+12,142	43,094	1,397,342	1,139	256,857	37,819,399
31	Armenia	171,227	+282	3,179	162,984	1,071	241,561	2,966,874
32	Chile	812,344	+4,472	20,310	770,190	1,057	478,756	19,223,423
33	Romania	791,971	+3,923	20,167	733,616	1,053	312,707	19,153,234
34	Luxembourg	54,871	+193	634	51,290	1,002	3,306,131	632,605
35	Bolivia	245,719	+1,339	11,547	189,832	980	59,247	11,776,791

We are finishing a multi-country study that proves without doubt that there is a lower Case Fatality Rate of COVID in high altitude residents. Furthermore, we don't understand why they think that Bolivia was one of the most affected countries. Bolivia as of Feb 25, 2021 ranked 35 in Death per Million inhabitants (see above), which we confirm on July 19, 2021. On Feb 24, 2021 USA had 1,565 , Chile= 1,057, Spain= 1471, Peru= 1,380, Italy= 1,605. France= 1309. From worldmeters.info. (see above). On July 19,2021 USA= 1,565 , Chile= 1,789, Spain= 1734, Peru= 5,834, Italy= 2,118. France= 1704. NOTE that all these countries of the people that sent the letter, are way above that of the Bolivia= 1475.

We have also shown previously the lower incidence and lethality at:

Zubieta-Calleja G, Merino-Luna A, Zubieta-DeUrioste N, Armijo-Subieta NF, Soliz J, Arias-Reyes C, Escalante-Kanashiro R, Carmona-Suazo JA, López-Bascope A, Calle-Aracena JM, Epstein M, Maravi E. Re: "Mortality Attributed to COVID-19 in High-Altitude Populations" by Woolcott and Bergman. High Alt Med Biol. 2021 Feb 9. doi: 10.1089/ham.2020.0195.

23. Perusing the list of references, it appears that roughly one third are from the author himself, and among them, most refer to data that have not undergone peer-review.

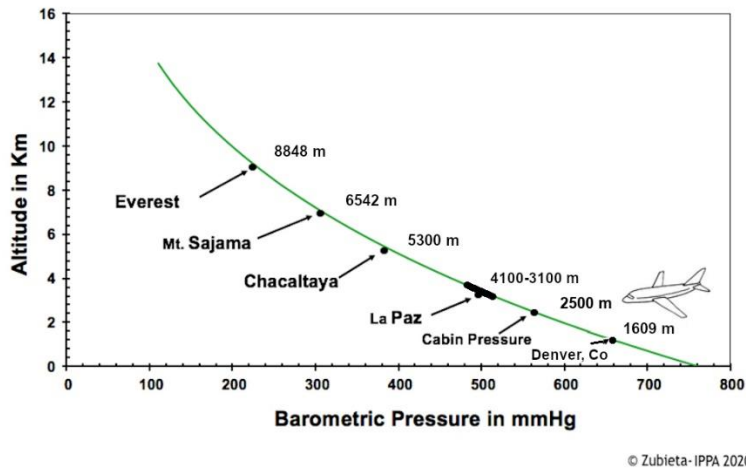
Response 23:

Well, first of all, we are two authors who have contributed to this paper. Several references being ours is true, but about a third of those were written and worked by the late Prof. Dr. Gustavo Zubieta-Castillo (Sr.). It is important to note that this paper is not a review. It is an article with our experience with these diseases, as born, living and working high Andeans, during 50 years. Moreover, we published our work, and we have been working on this subject for several years. It is based on those findings that we are writing this paper. But it also has to do with the fact that we disagree with several things they publish as we don't see it in our everyday medical practice. It is one of the reasons why we decided to write this paper. The majority of our papers did undergo peer-review. The authors of the letter to the editor against our paper are not the only high altitude experts around the world. Multiple researchers' work around the world agree with us, in their findings. Several distinguished scientists from Latin-American and the Himalayas are writing articles that are in our line of thinking. Should all their papers be retracted?

24. In figure 1, the point « La Paz » corresponds to two altitudes (city of La Paz 3,100 and El Alto 4,100 m) that should not be put on the same point on the curve, since 4100m is obviously different from 3,100 m in terms of barometric pressure and physiological effects.

Response 24:

Actually, we had corrected this graph, but somehow it was not uploaded for the final version.



On the other hand, unfortunately, they have not been to La Paz, as it is a bowl-shaped city ranging from 3,100 to 4,100m where the Altiplano (High Plateau) is located. There is no clear division as of everyday life activities between the cities. There are, however, acid-base changes with altitude for people going from 3,100m to 4,100m as we showed in our paper available at ResearchGate:

https://www.researchgate.net/publication/257306516_physiological_changes_related_to_rapid_altitude_shifts-La_Paz. It was published in Acta Andina and was peer-reviewed.

25. As noted above, the assumption of “Normal Acid-Base status” on top of figure 2 is erroneous.

Response 25:

Again, high altitude interpretation of Acid-base status needs to be correctly understood and corrected. They have to read our paper:

Paulev PE, Zubieta-Calleja GR. Essentials in the diagnosis of acid-base disorders and their high altitude application. J Physiol Pharmacol. 2005 Sep;56 Suppl 4:155-70. PMID: 16204789.

26. There is no argument for “increased mitochondrial efficiency”; there is no reference

associated with this purely speculative assumption.

Response 26:

To our surprise, we have not mentioned the “increased mitochondrial efficiency” in this paper. Nevertheless, we do agree there is increased mitochondrial efficiency, as we have just read a great paper that has just been accepted at Frontiers:

“Mice and rats display different ventilatory, hematological, and metabolic features of acclimatization to hypoxia”, by Christian Arias-Reyes, Jorge Soliz, and Vincent Joseph.

The mentioned paper does in fact, prove the increased mitochondrial efficiency. And there are several others.

27. Figure 4 on « breath holding » is beyond the scope of the paper and has no validated reference.

Response 7:

This observation has already been answered in #8.

28. What is the origin of the data in figures 5 and 6 concerning blood gas tensions in teenagers and “HAPE tongue”? There is no reference of corresponding published data.

Response 28:

The HAPE tongue has been published before in our book dated 1989:

The “Hape tongue”, previously described by us, is of great importance as it can significantly aid the diagnosis, although it is not always present (Zubieta-Calleja and Zubieta-Castillo, 1989).

All data we present is based on our data, taken in the Institute.

This supports a more extensive publication containing the data of 1865 patients:

Zubieta-Calleja G, Zubieta-Castillo G, Zubieta-Calleja L, Ardaya-Zubieta G, Paulev PE. Do over 200 million healthy altitude residents really suffer from chronic Acid-base disorders?. *Indian J Clin Biochem.* 2011;26(1):62-65. doi:10.1007/s12291-010-0088-9

Zubieta-Calleja, G.R., Zubieta-Castillo, G., 1989. High Altitude Pathology at 12,000 ft. Papiro. La Paz, Bolivia

Available at Mendeley and ResearchGate

https://www.researchgate.net/publication/344025807_High_Altitude_Pathology_at_12000_ft

NOTE:

Finally, we want to thank the detractors as their external review has helped us improve the wording and arguments written in the:

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

We have already edited our paper, answering all the “questionable points”.

It is also important to note that resulting from group peer-pressure, the point of view manifested by the writers of these questions and their language is quite aggressive and contrary to ours. It becomes evident that all those who signed the closed letter to the Chief Editor of RP&NB have a conflict of interest with this paper. This article does not follow their theories and articles blindly.

We have enough successful experience and data, and we will continue writing and publishing more about it. Hence, due to ethical values, we suspect they cannot be REVIEWERS to our papers. They have made it a systematic goal to reject everything we write. We think this has to do with the fact that we live and work in the marvelous city of La Paz at 3,500m.

This paper is a significant contribution and guide for physicians living at high altitude, treating high altitude illnesses; it is definitely not a threat to public health; quite the contrary, it will save many lives. *We base our lives and work on the fundamental principles of “**science, honor, and truth**”.* And, we are aware it is always a challenge to change the established paradigms, but we will persevere as we have complete confidence in our work. High altitude chronic hypobaric hypoxia should be understood and not feared.

For further inquiries, please feel free to contact us.

Sincerely yours,

Prof. Dr. Gustavo Zubieta-Calleja and Dr. Natalia Zubieta-DeUrioste
gzubietajr@altitudeclinic.com