COVID-19: Multiple diseases simulating extreme high-altitude exposure? Oxygen transport physiology and scarce need of ventilators; Andean Condor's-eye-view

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Abstract:

The critical hypoxia in COVID-19 patients during this pandemic, has taken away many lives all around the globe. The mechanism has been poorly understood and initially, word got around that it was a SARS (Severe Acute Respiratory Syndrome) pneumonia. The atypical images in lung computerized axial tomography (CAT) scans were alarming. This immediately alerted everyone including poor countries to purchase lacking sophisticated ventilator equipment. However, in some countries, even 88% of the patients on ventilators lost their lives. New observations and pathological findings are gradually clarifying the disease. What seems evident is that it is not only one disease but several, with different responses in different countries and different altitudes. The critical hypoxia and «gasping» present in some patients are not totally understood. It was mentioned that it could be like a High-Altitude Pulmonary Edema (HAPE). Hereby, as high-altitude medicine and hypoxia physiology specialists, we compare the pathophysiology with that of high-altitude exposure in order to understand the mechanisms involved. Some differences in lung radiological images along with transmission and viral attack mechanisms are discussed. The oxygen transport triad used at high-altitude can be applied on this pathology in order to propose even the use of erythropoietin (EPO) early in the treatment. The immune system is the most important long-term survival tool, so we suggest a short-term strategy: the use of special Earth open-circuit astronaut-resembling suits with effective outside air filtering re-breathing mechanisms in order to return to work and daily activities, without contamination risk. Thereby, the curve can be flattened without quarantine and the economy could recover.

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Introduction

The whole planet is suffering the merciless attack of the recent time most aggressive virus, the SARS-CoV-2. This pandemic, simulating a “Bio-Nuclear Attack” has taken all medical centers, governments and the population in general by surprise. The speed of the attack, the clinical characteristics, the imaging findings, the fast Case Fatality Rate reaching even more than 13 % of those infected[1], the intensive care units facing difficulties with an overload of patients, and the ventilator poor responses have indeed created havoc. All this because SARS-CoV-2 virus presents a hyper-exponential type progression. It is not a regular exponential progression ($y = A * B^x$), but rather an asymptomatic subject can initially transmit, variably, the disease to tens or more subjects in one environment[2]. The quarantine is a temporary break, but with great uncertainty. The possibility of developing a vaccine will take several months[3]. In this paper, we analyze the SARS-CoV-2 in its general characteristics of transmission, it’s binding mechanism and consequences in order to understand the hypoxic impact. Furthermore, similarities and differences with High Altitude Pulmonary Edema (HAPE) are interpreted through high altitude physiology, imagenology and medical experience at high-altitude. All suggestions have to be discussed in order to improve the understanding and treatment of this rapidly progressing situation that threatens the psychological, economical and general well-being of all humans.

What is the mechanism of transmission of CoV-2?

It has been well documented that SARS-CoV-2 can be very contagious as it is transmitted via droplets, aerosols and contaminated surfaces, but also when patients are still asymptomatic[4]. Initially it was thought to affect the elderly more, yet it was observed that youth, children and people with co-morbidities (overweight, diabetes, etc), are also included[5, 6]. This virus has a morphological shape described as a coronavirus. It has surrounding pointing spikes as shown through electron microscopy[7]. This shape is similar to some plant seeds that are lightweight and with pointed spikes, easily transported by wind and airborne until they fall randomly in a

suitable soil for reproduction. The greater the number of organisms, the greater the probability of reproduction thereby avoiding extinction. The same happens with the coronavirus. A 120 nm particle that has spikes can be airborne quite easily and possibly remain in flotation in an environment where an infected patient coughed or simply exhaled air[8]. It may even travel long distances through the air, in cloudy and windy days, when the U-V index is low, but this needs to be proved.

We suspect that the virus does not travel to the lung tissue through the walls of the trachea and the bronchi. It most probably has to arrive to the alveolar area through inhalation as suspended particles, due to its low nano-sized weight (120 nm). This would explain why there is a non-productive dry cough initially with no bronchial hypercrinia (hypersecretion) reaction. Hence it is fundamental that breathing in a contaminated environment (using masks) be carried out through the nose, avoiding deep mouth breathing. The nose plays the role of air warming, humidifying and essentially filtering within the bugles the dust particles and in this case the virus. The nasopharynx inflammatory process could not be so clinically evident with rhinorrhea and nasal breathing obstruction, but only anosmia[9]. It would be interesting to study if those with anosmia, have a better outcome.

As the center of the virus remains distant from the contact area through the spikes, this grants it a greater survival on surfaces. A brilliant and outstanding design of nature. The time of survival on surfaces have been amply reported[10]. Noteworthy is the fact that there is less survival time in copper surfaces. Copper is a metal with similar electrochemical characteristics of silver and gold in the periodic table. Why do copper surfaces reduce the survival time of coronavirus? Copper may produce viral lysis through an electric potential due to its electro-magnetic characteristics that can act as a battery as Volta well showed[11].

SARS-CoV-2 reduces both ventilation/perfusion and invades other tissues

Covid-19 patients can suffer a fast-evolving dyspnea and this becomes an alarming “gasping”[12]. Much like fish pulled out of their natural environment: water. So, the

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process can evolve to an acute pulmonary insufficiency associated to tachycardia. What gives rise to this condition? A reduction of the ventilating surface area, in our criteria, due to loss of alveoli and the contiguous capillary tissue[13]. The virus attacks the alveolar cells producing diffuse alveolar-capillary damage. SARS-Cov-2 has also been found in blood as RNA as well as in fecal and urine samples[14]. Initially entering through some Angiotensin-converting enzyme 2 (ACE2) receptors of mostly lung epithelial cells, it is possible that it triggers the Nuclear Factor-kappa B (NF-kB) signaling and a cytokine storm response as shown in previous SARS-CoV infected patients[15]. This can be assumed from the fact that COVID-19 patients presented significantly elevated proinflammatory cytokines and chemokines such as tumor necrosis factor, interferon gamma-induced protein-10, interleukin-6, interleukin-1beta, granulocytes-colony stimulating factor, monocytes chemoattractant protein-1 and macrophage inflammatory protein-1alpha[14]. Equally, an immune thrombotic syndrome has been described based on autopsy findings of inflammation, formation of hyaline membranes, mononuclear cells, macrophages infiltrating air spaces and diffuse thickening of the alveolar wall, along with lesions in spleen, liver and kidney[13, 16]. So, there is a great reduction of both oxygenation factors: ventilation/perfusion. Hence, the rest of the still healthy and functional lung tissue tries to compensate this deficiency, yet SARS-CoV-2 continues the invasion and multiplies. The rupture of capillaries give rise to local hemorrhages, yet we don't know if these patients present anemia[16]. Patients suffering from anemia can be more seriously affected by CoVid-19. Some reports show that coughing can give rise to blood stained sputum, as seen in thromboembolism and HAPE[17]. Noteworthy is that COVID-19 is not a highly sputum productive pathology. The possible explanation for that is that the virus, does not migrate through the cilium in the trachea and bronchi with little or no affinity for those cells, even though ACE2 receptors have been found in bronchial transient secretory cells[18]. Autopsies however, show clear bronchi[16]. It can attack the oral mucosa[19] and the olfactory system, leaving several with anosmia[9]. The virus travels to the alveoli through the inspired air and implants itself in the alveolar-capillary membrane in the ACE2 receptors[20]. As lung blood capillary vessels are damaged, there is a strong possibility that SARS-CoV-2

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enters the blood stream at this site. ACE2 receptors are also found in the endothelium in vessels[21]. We suspect that what is being considered coagulation disorders, may actually be ACE2 receptors in the endothelium being attacked by the SARS CoV-2 and thereby generating coagulum in order to “cover” the endothelial lesions[22]. Indeed, during an inflammatory response, binding sites on the endothelial membrane are more exposed[22]. The cerebro-vascular accidents, heart myocardial infarctions and other obstructive ischemic lesions would arise from these endothelial viral attacks. Atypical vascular dynamics[14] could be due to SARS-Cov-2 binding to ACE2 receptors producing an imbalance of ACE1 (intact) and ACE2(interfered) in the Renin-Angiotensin-Aldosterone system.

The reduction of the pulmonary area of gas exchange needs to be properly understood. It is evident that patients evolve to present gasping and extreme hypoxia with cyanosis. The lung has a surface area of around 90 square meters, similar to the size of a tennis court. We previously described it as a parachute that if intact, allows the air to sustain the weight of the subject and decelerate adequately[23]. As the parachute with holes would not be able to hold the paratrooper, in a similar manner the infected lungs could not carry out an efficient gas exchange. In COVID-19, initially, the direct viral attack to alveolar-capillary membranes produces a gradually increasing hypoxia. Much like ascending to high altitude, hyperventilation ensues. $PaCO_2$ is maintained at sea level values until the functioning pulmonary surface area cannot ventilate enough to reduce it. Recall that CO_2 is 20 times more diffusible than oxygen, but this threshold is surpassed. Hypoxia increases and reaches a point where“gasping”begins.This condition simulates a rapid high-altitude ascent, like reaching Mt. Everest while at sea level. The highest point reachable in extreme hypoxia where life is possible[24]. But if the gas exchange surface area is compromised severely, with the resulting edema, inflammation, local bleeding, transudates and exudates (an atypical HAPE-type reaction with or without superinfection) on a sea level hemoglobin count or anemia, and pulmonary hypertension(creating more capillary stress failure), the hypoxia becomes severe. The subject initially hyperventilates and when hypoxia becomes very severe, he begins gasping for breaths in the final stages[25]. Ventilator assistance would be of limited use, and increased positive end-expiratory pressure (PEEP) would be detrimental in the

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dissolved alveolar tissue and can even lead to localized pneumothorax areas, thereby aggravating more the clinical condition[26]. Fever could result from cytolysis and liberation of intracellular components, including sialic acid from rupture of red blood cells and possibly other intracellular enzymes, cytokines and pirogens[13].

Similarities and differences with High Altitude Pulmonary Edema (HAPE)

With respect to the use of ventilators in COVID-19, it has been found that SARS type treatment is not very effective[26]. Some even suggested that the COVID-19 would be similar to HAPE and hence patients could receive the same treatment[27]. The characteristics of HAPE are ascent to high-altitude, shortness of breath, coughing, cyanosis, hypoxemia, headache, tachycardia, tachypnea, discrete rales and blood-stained sputum sometimes. Most symptoms resemble those of COVID-19. Apparently there are some reports of in-situ high-altitude HAPE[28], but we have never seen it in the city of La Paz in Bolivia (4,100-3,100m). Those reports of HAPE without descent are most probably a form of atypical pneumonia that has different characteristics due to pulmonary hypertension at high altitude, and in different latitude and longitudes, thereby changing the radiologic imaging. However, the pathophysiology of HAPE is totally different to COVID-19.

In COVID-19 it is best to run a CAT scan as it gives very precise images, whereas in HAPE a chest X-Ray is more than enough, generally. The HAPE chest X-Rays presents unilateral or bilateral cotton-like images that are patchy, diffuse, fuzzy and irregular in their distribution (Fig. 1). It is edema in the alveolar sacs but with the alveolar-capillary structures unaltered except in very few spaces, due to high permeability edema and barometric pulmonary hypertension stress failure[29]. In COVID-19, the CAT scan shows atypical, irregular, clear and delimited dense images in the initial stages but these then evolve to be complex and heterogeneous(Fig. 2). These “strange images” have been referred to, following the standard X-Ray terminology, as “ground glass”[30]. Ground glass is an area of increased attenuation in the lung with preserved bronchial

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and vascular markings. However, it has truly called our attention as the images a very peculiar in shape and density. One can observe that there are clear borders with no bronchial and vascular markings and we believe this image should rather be called “Sheer curtain” as it is quite uniform in the initial stages(Fig. 3). Later on, it becomes more heterogeneous and a ground glass type image. This has extremely important implications for the interpretation of this novel disease and requires a new radiological classification. The virus destroys the alveolar-capillary tissue and there is edema, possibly hemolysis, hemorrhage, and in some long-lasting cases pus from superinfection. In both pathologies, the increase of the FIO_2 will raise the blood gases PaO_2, but not as effectively in COVID-19 as compared to HAPE[31]. Above all, the HAPE process resolves quite fast in children (1-2 days) and a little longer in adults (3-5 days) with full radiologic clearance. But what is fundamental is that, although there is a dilated right ventricle and pulmonary hypertension in HAPE, once resolution is achieved there is a normal lung function without any residual sequelae at the same altitude and also upon returning to sea level or even ascending afterwards to the summit of Mt. Everest[32]. Whereas in COVID-19, the coronavirus produces “alveolar-capillary cytolysis” and the intense inflammatory-immunological response destroys the lung tissue. In around 25% of the cases there is also heart muscle compromise[33, 34]. Likewise, COVID-19 has a longer, more dramatic and destructive evolution.In the recovery process it canresult in a reduced pulmonary function and end up limiting the exercise capacity. At high-altitude, COVID-19 sequelae can result in a compensatory increase of the red blood cells, a secondary polycythemia that would be interpreted by most as Chronic Mountain Sickness or what we callpoly-erythrocyt-hemia (Poly=many, Erythrocyt=RBC’s, Hemia=in blood)[35]. Some have reported, following the pathological studies, that there is a pulmonary thrombosis not typical in SARS[36]. There are suspicions of a disseminated intra-vascular coagulation, i.e. a severe clotting disorder[5]. The alveolar-capillary destruction, would give rise to a “fluidification” of the area that would, in our understanding generate an intense inflammatory reaction that could alter the coagulation system. This could possibly give rise to the aforementioned atypical “Sheer curtain” images in well-defined areas in the CAT scan. In other words, due to the

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speed of the viral attack to the lungs, there is a massive self-destructive immune response depending, of course, on the amount of inoculation of the coronavirus. Endothelial damage through the ACE2 receptors could also generate inflammation and coagulum formation. Furthermore, COVID-19 presents initially with a dry cough that is very irritating along with fever that accelerates heart rate, also aggravated by progressive hypoxia. The increased cardiac output, complicates pulmonary function. COVID-19 is also associated to muscular body pain that brings along adynamia, discomfort, anorexia and sometimes diarrhea[37]. Hyperventilation, fever, sweating, diarrhea, can give rise to dehydration, which can induce a further complication of thromboembolism.

The COVID-19 incidence at high altitude

It seems that the progression of COVID-19 in high altitude populations (China, Bolivia, Ecuador, Colombia and India) is slower[38] and therefore the incidence is lower. The “extreme” Ultra-Violet Index radiation at high altitude due to decreased filtering of the thinner atmosphere, could play a role[39]. Furthermore, we have recently co-authored a paper, by Laval University members, postulating that since high altitude residents have a down-regulation of ACE2, being this the area of viral attack in cells, they would be less susceptible to infection[38]. In Fig. 4 it can be seen that the Bolivian cities above 3,000m, have a slower increase in reported positive cases compared to Bolivian lowlands[39]. Undoubtedly, many variables play a role in the evolution of the disease. The speed of quarantine establishment, compliance of the people, the enforcement, the use of face masks and hygiene, the speed of isolation of suspected infected people, the speed of testing for coronavirus, the tests availability, the nutritional conditions, the genetic strength, co-morbidities, immune system conditions, environmental conditions (temperature, dryness, U-V radiation at high altitude) and previous exposition to other coronaviral diseases. In India, there are fewer cases at and above 1,000 m with lower incidence in spite of huge populations like in Bangalore compared to sea level cities like Mumbai, Chennai or even Kerala.

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The Oxygen Transport Triad at high-altitude

Fig. 2 is from a COVID-19 patient in the city of El Alto, at 4100m, a miner who had a previous lung injury several years back from toxic substance inhalation. The current CAT scan shows extensive lung compromise. He was transferred to an ICU, placed on a ventilator and after several days, passed away. Understanding high-altitude hypoxia and its adaptive mechanisms can help clarifying the serious complications that SARS-CoV-2 is giving rise to. The physiological oxygen transport system can be represented as a triad: 1) the pneumo-dynamic pump (ventilation), 2) the hemo-dynamic pump (the heart), and 3) the erythropoietic system (hemoglobin)[35]. All three function together in order to transport oxygen to the tissues. This triad is like a tripod. When a sea level dweller ascends to high altitude, the Partial Inspired Oxygen Tension (PIO_2) drops, and oxygen is assimilated in the body “by diffusion and by diffusion alone”, quoting August Krogh[40]. However, the metabolic processes of cellular life must adapt to the low barometric pressure.

1) Pneumo-dynamic pump

The first response to high-altitude exposure is hyperventilation[41] (an increase of the pneumo-dynamic pump), based on a higher respiratory frequency and higher tidal volume, particularly during temporary dyspneic episodes due to sudden uphill climbs or any other exercise that demands more oxygen. Hyperventilation at rest at high-altitude does not fully compensate the decrease of the PIO_2[23]. If we assume a resting sea level ventilation of 4.82 L/min/m2 according to the Ideal Gas Law, PV=nRT (where P=Pressure, V=Volume, n=Avogadro’s number, R=Ideal gas constant and T=Temperature), if nRT remains constant then in order to expose the pulmonary area to the same number of oxygen molecules at high altitude (3600m) following Boyle’s Law, then:

$$P1*V1 = P2*V2$$

$$\text{Sea Level Pressure} * \text{Ventilation Volume} = \text{3,600m La Paz Pressure} * V2$$

$$(760\ \text{mmHg}) * (4.82\ \text{L/min/m}^2) = (495\ \text{mmHg}) * V2$$

$$V2 = 7.40\ \text{L/min/m}^2$$

In reality, the average resting ventilation at 3,600m is 5.07 L/min/m^2, so the actual number of oxygen molecules exposed to the lungs is 1/3 less than at sea level and

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hence a PaO_2 of 60 mmHg (instead of the sea level 95 mmHg) is also 1/3 less. A high permanent hyperventilation is not possible as that there would be respiratory muscle fatigue and excessive respiratory alkalosis, unacceptable for optimal cellular metabolism. This is confirmed in the breath-holding test performed in La Paz, where the normal SpO_2 of 90% rises after a deep breath to around 98% (sea level values) in normal subjects[42, 43]. Artificial ventilation benefits from this physiological response, but not as efficiently when there is pulmonary destruction.

2) Hemo-Dynamic pump

The other functional adaptation factor is a hyperactivity of the heart (hemo-dynamic pump). The heart rate and stroke volume increase along with pulmonary hypertension and sometimes systemic arterial hypertension. All these, in order to improve perfusion and thereby allow a faster oxygen transport.

3) Erythropoietic system (Hemoglobin)

The 3rd component is the erythropoietic system that regulates the production of hemoglobin, the iron-containing oxygen-transport metalloprotein. Upon arriving to high altitude, there is a logarithmic increase of the hematocrit until a maximal optimal plateau is reached[44].

Furthermore, for anyone at high-altitude (resident or visitor), the Tolerance to Hypoxia formula shows that paradoxically, the higher the altitude, the higher the tolerance to low levels of oxygen (low PIO_2) when there is an optimal acid-balance balance and THID=0 (BE=0)[45][46].

Tolerance to Hypoxia=(Hemoglobin/$PaCO_2$)* 3.01

The formula has 2 fundamental variables and a constant:

A) The numerator (Hemoglobin) represents the metabolic component of the formula that **takes time to develop**. It is the most sustainable functional support of the triad of oxygen transport. It is not an immediate response. For an altitude like La Paz-Bolivia (3,600m) it takes around 40 days to reach an optimal hemoglobin level. The cardio-respiratory pumps are gradually relieved of the over demand. Over those 40 days, dyspnea gradually decreases during exercise.

B) The denominator ($PaCO_2$) represents the respiratory component of the formula. It **changes immediately** upon arrival to high altitude through hyperventilation. For

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example, the normal sea level $PaCO_2$of 40 mmHg is reduced to 30 mmHg at the altitude of 3,600m in the city of La Paz. A higher $PaCO_2$ decreases the affinity of the hemoglobin oxygen dissociation curve (the Bohr effect).

C) The constant 3.01 of the formula is derived by dividing the normal sea level Hb 13.3 gm by the normal PaCO2 = 40 mmHg and equating it to 1:

K *13.3/40=1. This sets the tolerance to hypoxia at sea level as 1. As the altitude increases, the normal Hb and PaCO2 values at each altitude provide the tolerance factor. For La Paz, (3,600m) and Mt. Everest (8,842m) it is 1.7 and 4.86 times more tolerance, respectively. This means a person on the summit of Mt. Everest is able to tolerate hypoxia nearly 5 times more than at sea level, without losing their life in a PIO2 of 43 mmHg.

$PaCO_2$ plays a fundamental role in the acid-base status of blood, according to the Henderson-Hasselback equation. From the sea level point of view, a high-altitude low $PaCO_2$resulting from hyperventilation is interpreted as Respiratory Alkalosis (with a pH, above the normal values), that needs to be compensated. One way would be to decrease ventilation in order to increase $PaCO_2$ but that would compromise oxygen capture as stated above. So, a metabolic decrease of the balancing bicarbonates through renal compensation is the only feasible mechanism. Once a stable pH = 7.4 is reached in around 1 or 2 days, the organism is in its optimal metabolic state at 3,600m. This is a normal acid-base balance for high altitude, and not a chronic respiratory alkalosis. Some authors have found that a mild alkalotic pH remains for a longer time in sea level travelers to5,000m, as compared to residents. but other variables have to be considered, like a pre-existent anemia[44]. Sea level acid-base interpretation charts, such as the Sigaard-Andersen or the Davenport Nomograms give the wrong interpretation at high altitude, and should not be used. Hence, we developed high altitude correction factors for the Van-Slyke equation and the Acid-Base Nomogram[46]. We also established clearly that it is not possible for over 200 million inhabitants at high altitude to live in a permanently abnormal acid-base status[47]. In other words, the new acid-base status at high altitude is the normal condition (as at sea level) and a fundamental part of survival.

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An SpO_2 of 90% with a PaO_2 of 60 mmHg are normal values for the high-altitude residents in the city of La Paz, Bolivia (3,100-4,100m)[48]. So, this is definitely tolerable. However, we have the advantage of a raised compensatory hematocrit with an adequate acid-base status and pH.

In Chronic Mountain Sickness (or what we call Poly-erythrocyt-hemia), there is always a decreased PaO_2 with respect to normal high-altitude residents[35]. Pulmonary function is compromised with shunts, ventilation/perfusion inequality, hypoventilation and lung oxygen diffusion alterations. The only possible compensating mechanism in order to sustain an adequate oxygen tissue supply, becomes the increase of hemoglobin, i.e. the 3rd pillar of the triad[35]. Consequently, we believe there is no excessive increase of red blood cells but rather the only way out to survive disease in a chronic hypoxia environment[35]. And likewise, the most energy efficient mechanism[47]□□.

The oxygen transport triad, treatment and the use of ventilators in COVID-19

Blood gases in a sea level COVID-19 intubated patient reported pH = 7.19, $PaCO_2$ = 70.1 mmHg, PaO_2 = 63.7 mmHg and bicarbonates 26.0 meq/L. This is truly a critical condition. The diagnosis would be severe respiratory acidosis with very high $PaCO_2$ (the denominator) and hence very low tolerance to hypoxia leading to a fatal outcome. In another case in Arequipa-Peru (2,335m), an11-year-old girl losther consciousness in the harvesting fields. She was found to be COVID-19 positive. Her blood gases reported: pH = 7.00, $PaCO_2$ = 116.9 mmHg, PaO_2 = 152 mmHg, Ht = 47% and Hb 15.4 g/dl. A severely elevated $PaCO_2$pattern, and at high altitude signifies a greater risk of low tolerance to hypoxia. She was intubated at the ICU and presented nighttime hypoxemia (on FIO_2 = 100%) alternating with daytime improvement and reduction of FIO_2. The last blood gases at the moment of expiration, while being ventilated, reported: pH = 6.96, $PaCO_2$ = 30.5 mmHg, PaO_2 = 235 mmHg, Na = 135mmol/L, K = 5.36mmol/L, Ca = 0.59mmol/L, Cl = 91mmol/L. Lactic Acid=19.7 mmol/L (0.5-1.5), Ht = 12% (Data courtesy of Dr. Diego Grajales López). The diagnosis in the final stages when she presented 20,000 leukocyteswould be severe metabolic acidosis. The PaO_2 is high but the oxygen content, would be very low associated to a cardio-vascularfailure, low

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hematocrit and metabolic failure. Both cases have a failure of the oxygen transport triad, as observed.

In COVID-19, the fundamental three components of the oxygen transport triad are all compromised in a very short time (around 1 week). The dyspnea becomes intense, the tachycardia very important and fundamentally on a low hemoglobin count, the situation becomes critical. Hence the hypoxia becomes severe and life cannot be sustained.

If the functionality of one of the triad components of oxygen transport is reduced, the other two can try to compensate by increasing their work or number (in the case of RBCs). What can be done? The immediate treatment protocol strategy would be to increase the FIO_2, of course in an attempt to reduce hyperventilation and eventual “gasping”, which is a final survival reflex. Although hyperventilation has been associated to the removal of the excessive $PaCO_2$, the deep breaths associated to it can also give rise to a higher SpO_2 and hemoglobin oxygen capture[42]. The hemo-dynamic pump can also be stimulated but with much lower significance. The most feasible solution would be to increase the hemoglobin, as happens with exposure to chronic hypoxia. Thereby a high hemoglobin count reduces the work of the pneumo-dynamic and the hemo-dynamic pumps. Therefore, it could be a wise strategy that as soon as a patient presents the first symptoms of coronavirus, an initial dose of erythropoietin (EPO) be given, then after 3 days a second dose be repeated. The idea would be to increase the hemoglobin and hematocrit so that there is a reserve if the lung and heart get compromised. This explains what happened in a case where EPO was given and recovered successfully[49]□. Hemograms performed in a hospital of the city of El Alto-Bolivia (4100m) with 1 million inhabitants, presented hematocrits above 56% in 52% of males and 26% of females. These people carry out normal lives, so there should be no fear to increase the red blood cells[35]. Blood transfusions would also help in the more acute and severe stages. This would give the immune system time to defend the organism against the SARS-CoV-2. The sooner EPO is given (due to the delay time of RBC, Ht rise), the better. EPO also has been shown to increase tolerance to hypoxia in the brain[50]. Another possibility would be the use of a heart-lung machine in order to artificially oxygenate blood but this is truly limited to very few cardiologic surgery centers.

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In fact, in order to treat COVID-19 it would have been much better to equip Intensive Care Units with heart-lung machines than ventilators.

The management of patients with lung compromise is to improve the oxygen supply. The initial procedure is to raise the FIO_2 until an adequate pulse oximetry level is achieved:> 90% SpO_2 at sea level and > 80% at high altitude (3,600m). This could reach a FIO_2 of 100% and still be insufficient for an adequate oxygen transport, if the lung compromise is severe, giving rise to oxidative stress. A hyperbaric chamber could increase the dissolved oxygen pressure but not in a very effective way in order to cover the oxygen demand. If the SpO_2 drops below the 50% levels, the condition becomes critical at sea level. Hemoglobin levels become fundamental and can be raised to very high levels, until the critical condition is surpassed, depending on the degree of pulmonary tissue destruction, provided there are no coagulation alterations or if coagulation is under control. Life is possible with only one lung, which is 50% of functional lung tissue, but it requires time for adjustment. Surpassing the acute stage, there would be limitation for exercise and a compensating poly-erythrocyt-hemiawould develop. But this would be a last chance survival strategy. Several would have to live permanently on supplementary oxygen. Some could have a lung transplant, but this has several limitations aside from high costs. The heart can also be compromised[34, 51]. This, in our criteria, could be the result of a transfer of the virus through the capillaries (viremia) to the left ventricle, or coagulation alterations producing inflammation or myocardial infarction. The second component of the triad is compromised and would severely aggravate the situation.

Anti-inflammatory drugs could be used early in the treatment in order to avoid the excessive immune reactions compromising the triad[13]. Being tops the Acetyl-Salicylic-Acid as it is an analgesic, anti-inflammatory and anti-platelet aggregation factor, provided there is no allergy or adverse reactions. Monitorization of pulseoximetry early in the disease can indicate the requirement of oxygen via nasal prongs so as to avoid hypoxia and pulmonary hypertension. Adequate oral hydration, antibiotics for control of superinfections are fundamental, likewise.

Is a ventilator useful under these conditions? Ventilators are mostly necessary incentral nervous system structural and functional alterations, neuromuscular disorders,

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obstructive and restrictive diseases (like ARDS),surgery under anesthesia, post-surgery recovery, during coma or unconsciousness, collapsed lung, brain injury, COPD, drug overdose, Guillain-Barre syndrome, myasthenia gravis, pneumonia, polio, stroke and upper spinal cord injuries and others[52]. SARS-Cov-2 falls into none of these, with minor individual case exceptions. The fundamental role of ventilation is to move air into the lungs, allowing oxygen input and removing carbon dioxide. Risks of the use of ventilator include infection, vocal cord issues, lung injury by the use of too much pressure, pneumothorax, even oxygen toxicity and maybe thromboembolism. We believe ventilator use is very limited in COVID-19 patients. It has been advised that low pressures be used in ventilators, only if they are absolutely necessary[26]. Many cases that were put on ventilators remained over 3 weeks, with bad prognosis. In New York City 88.1% of those on ventilators died[53]. Weaning in those cases becomes very difficult if not impossible. The low hemoglobin, and a high $PaCO_2$ both linked to a deficient hemo-dynamic pump, greatly reduce “tolerance to hypoxia” and make life unsustainable. This implies that increasing the hemoglobin in the shortest time possible could allow for a better survival rate. It would simulate a high-altitude biological response to low oxygen pressure provided the pH is maintained within normal values, and $PaCO_2$ is effectively reduced by hyperventilation.

The idea of “respiratory rest” is fundamental for the treatment if the PaO_2 can be sustained at acceptable limits, provided there is enough alveolar surface area. Unfortunately, sever cases evolve beyond that point.

COVID-19 are multiple diseases. Is the SARS-CoV-2terminology correct?

It seems evident that the name SARS-CoV-2 only pertains to one aspect of the multiple diseases induced by this virus. Because of the SARS terminology, intensive care units have rushed to use ventilators. However, this viral disease can actually also be a SAHS-CoV-2 (Severe Acute Heart Syndrome), and/or SAAS-CoV-2 (Severe Acute Anemic Syndrome), and/or SACS-CoV-2 (Severe Acute Coagulation Syndrome), and/or SAIS (Severe Acute Inflammatory Syndrome), and/or SACS-CoV-2 (Severe Acute Cerebral Syndrome) or other variants. It seems that the individual response to CoV-2

could be moderated by genetics, life style, nutrition, stress, exercise or sedentary condition, obesity, dehydration, inflammatory processes, processed food, exposure to toxic substances such as insecticides, chemical fertilizers, medication, chronic diseases, previous exposition to other viral, bacterial, parasitic or fungal diseases, area of major compromise in the lung, viral pathogenesis and possibly other aspects.

This is why the outcomes can be so catastrophic as the diseases are not being clearly understood. Following pre-established protocols in all patients is questionable because it is not one disease, it is several. Within the Gauss Distribution, the diseased population falling in the extremes has the worst outcomes. We have previously postulated a similar concept in relation to Chronic Mountain Sickness[35]. It is not one disease but rather multiple diseases in a chronic hypoxia environment. The Poly-erythrocyt-hemia is a physiological response of survival where diseases produce a reduction of the PaO_2 and the hemoglobin is in the steep part of the oxygen dissociation curve.

A pragmatical strategy

The fact of the matter is that CoV-2 has overtaken the planet. The main problem of these diseases is the irreversible progressive tissue damage, more than hypoxia itself if not lethal. What the world desperately needs is a way to destroy the virus. An effective vaccine is distant for the moment and likewise a viral treatment[54]. A temporary best solution is to avoid exposure and a permanent one is to have a good immune system. SARS-CoV-2 is like an alien. We need to isolate ourselves from the contaminated air we breathe. We propose that in order to save the economy, everyone should don an Earth astronaut-type suit with its own open-circuit electrically filtered breathing units and go back to work. Mass production of very economical suits is possible so that poor people also have access. The good thing is that it is an air exchange with the outside environment whereas in outer space it is a closed re-breathing complicated and expensive system, because there is vacuum and no oxygen. On arrival home, people should take off the suit in a safe way, with disinfecting showers and all other infection avoidance measures. This way it does not matter if someone never had the COVID-19

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nor if thosethat have it can transmit it. The hospitals could manage the severe cases more gradually until our immune system takes over.

Conclusions

The COVID-19 is a formidable challenge for human survival. Knowledge on high-altitude hypoxia physiological adjusting mechanisms can help understand these multiple diseases caused by CoV-2 and change therapeutic strategies. HAPE and COVID-19 are not the same. The pathogenesis and radiologic imaging have been differentiated. ACE2 location sites and their function are fundamental in order to understand the pathophysiology. The Oxygen Transport Triad is fundamental for understanding resulting hypoxia and the treatment of these diseases. Increasing the 3rd component of the oxygen transport triad through the use of erythropoietin and/or blood transfusions could improve outcomes while immunity develops[49]. Anticoagulants, antibiotics, anti-inflammatory medication, oxygen and hydration are advised. No fixed protocols of treatment for all should be used. A possible strategy in order to return to work, fundamental to avoid social conflict, would be to use an economical Earth open-circuit respiratory air filtering whole-body suit. The planet, for the moment, no longer belongs to us, humans. It belongs to CoV-2 until our immune system is able to fully overcome it.

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Figure Legends

Figure 1. HAPE chest X-Rays, from a young man (left) and an adult (right) in the city of La Paz-Bolivia (3,500m).

Figure 2. CAT scans of COVID-19 patient at high altitude who was a permanent resident of 4,100m in the city of El Alto. (Photo courtesy of Centro EspecializadoenTomografias - CET).

Figure 3. CAT scans of COVID-19 patient 11 years old form Arequipa-Peru, with severe lung compromise showing the“Sheer curtain”images. (Photo courtesy of Dr. Diego Grajales López).

Figure 4. Progression of the CoV-2 virus in Bolivia. The dashed lines correspond to the cities located above 3,000m of altitude. An updated figure until the end of the pandemic can be accessed at http://altitudeclinic.com/blog/2020/04/covid-2-bolivia/

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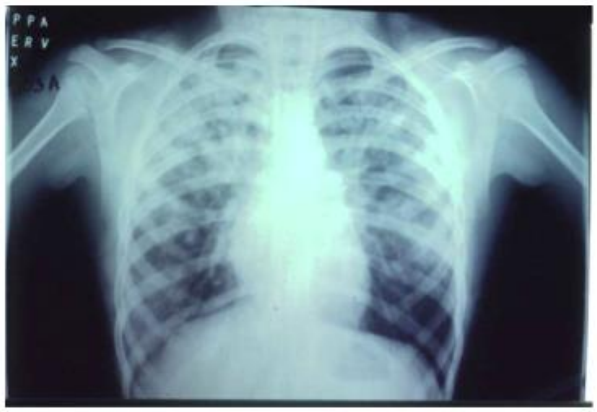
Figure 1.

HAPE young man



HAPE adult man

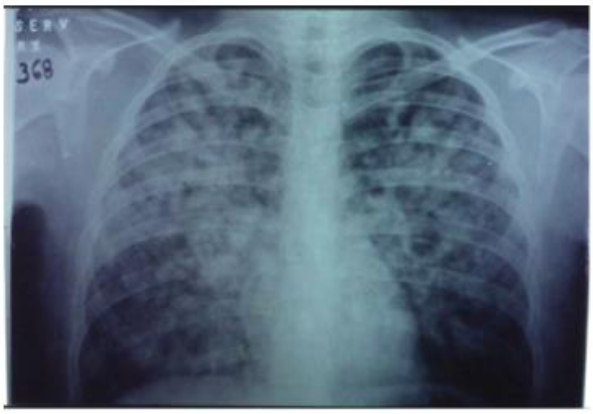


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Figure 2.

CAT scans of COVID-19 patient at 4,100m altitude

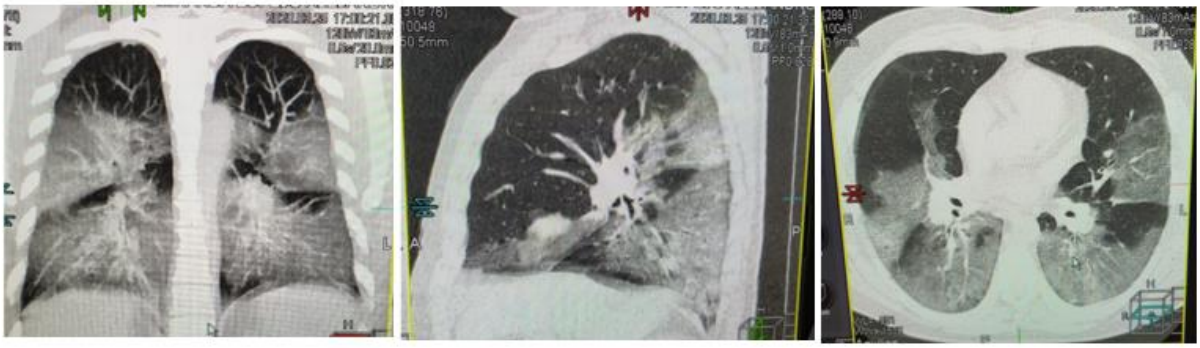

Figure 3.

CAT scans of COVID-19 patient 11 years old from Arequipa-Peru (2,335m altitude)

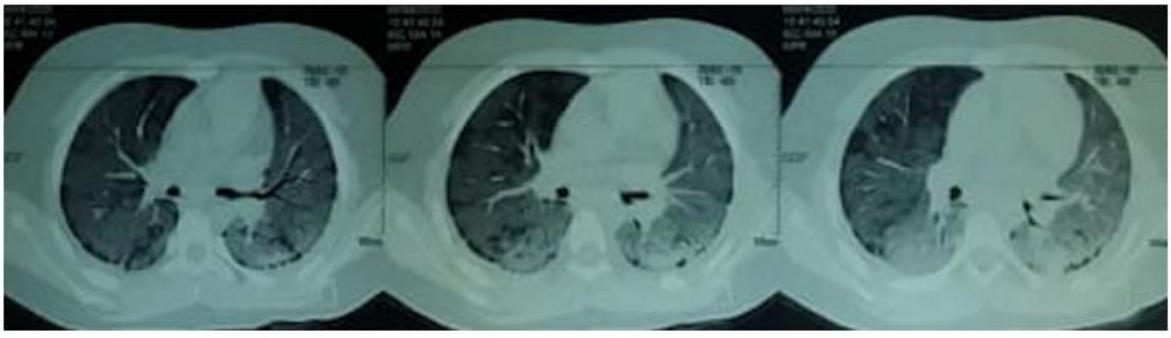

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Figure 4.