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Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude?

Christian Arias-Reyes[a], Natalia Zubieta-DeUrioste[b], Liliana Poma-Machicao[a], Fernanda Aliaga-Raduan[a], Favio Carvajal-Rodriguez[a], Mathias Dutschmann[c], Edith M. Schneider-Gasser[d], Gustavo Zubieta-Calleja[b,⁎⁎,1,2], Jorge Soliz[a,b,⁎,1]

[a] Institute Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ), Faculty of Medicine, Université Laval, Québec, QC, Canada
[b] High Altitude Pulmonary and Pathology Institute IPPA. La Paz, Bolivia
[c] Florey Institute of Neuroscience and Mental Health, Gate 11 Royal Parade, 3052, University of Melbourne Victoria, Australia
[d] Institute of Veterinary Physiology, Vetsuisse-Faculty University of Zurich, Winterthurerstrasse 260, Switzerland

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ABSTRACT

In the present study we analyze the epidemiological data of COVID-19 of Tibet and high-altitude regions of Bolivia and Ecuador, and compare to lowland data, to test the hypothesis that high-altitude inhabitants (+2,500 m above sea-level) are less susceptible to develop severe adverse effects in acute SARS-CoV-2 virus infection. Analysis of available epidemiological data suggest that physiological acclimatization/adaptation that counter-balance the hypoxic environment in high-altitude may protect from severe impact of acute SARS-CoV-2 virus infection. Potential underlying mechanisms such as: (i) a compromised half-live of the virus caused by the high-altitude environment, and (ii) a hypoxia mediated down regulation of angiotensin-converting enzyme 2 (ACE2), which is the main binding target of SARS-CoV-2 virus in the pulmonary epithelium are discussed.

1. Introduction

The SARS-CoV-2 virus, the pathogen causing COVID-19, infects its host cells by recognizing the angiotensin converting enzyme 2 (ACE2) (Lu et al., 2020). ACE2 is a trans-membrane protein located in the cells of the respiratory tract, lung, heart, arteries, veins, kidney and intestines (Hamming et al., 2004). In the pulmonary epithelium ACE2 acts as a vasodepressor, balancing the action of its counterpart the homologous enzyme ACE1 which acts as vasoconstrictor, and both enzymes form the oxygen-sensitive renin-angiotensin-system (RAS) (Hampl et al., 2015). In normoxia, the RAS system is regulated by the dynamic equilibrium between the expression of ACE1 and ACE2. However, under chronic hypoxia (O_2 2% for 12 days) ACE1 is upregulated by the hypoxia-inducible factor 1 (HIF-1) (a master regulator of the response to hypoxia) in human pulmonary artery smooth muscle cells (hPASMC), while the expression of ACE2 is markedly decreased (Zhang et al., 2009). Similar results were obtained in rats (males, SD) exposed to conditions equivalent to 4,500 m of altitude, which after 28 days showed increased levels of ACE1 and decreased expression of ACE2 in heart cells (Dang et al., 2020). These observations are highly relevant for the pathogenesis of COVID-19, since the level of expression of ACE2 in pulmonary epithelial cells has been demonstrated to be positively correlated with the rate of infection of the first SARS-CoV (Jia et al., 2005; Lu et al., 2020; Ren et al., 2020; Rothan and Byrareddy, 2020). These studies clearly may suggest that high-altitude inhabitants (i.e., chronically exposed to hypoxic conditions) express reduced levels of ACE2 in their lungs (and other tissues). Thus, succesful acclimatization to high-altitude environment could render local inhabitants less susceptible to SARS-CoV-2 virus penetration and consequently are protected from the development of the disease defining acute respiratory distress syndrome.

2. Methods

We analyzed the epidemiological data in: (i) the Tibetan region of China, in which the peak of the epidemic is over (no more domestic

⁎ Corresponding author at: Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ), 2725, chemin Sainte-Foy, High Altitude Pulmonary and Pathology Institute IPPA, Québec, QC, G1V 4G5, Canada.
⁎⁎ Corresponding author at: High Altitude Pulmonary and Pathology Institute IPPA, Av. Copacabana - Prolongación # 55, Teleféricos Celeste y Blanco Av. Del Poeta, La Paz, Bolivia.
E-mail addresses: gzubietajr@gmail.com (G. Zubieta-Calleja), jorge.soliz@crchuq.ulaval.ca (J. Soliz).
[1] Both senior authors contributed equally.
[2] www.Altitudeclinic.com.

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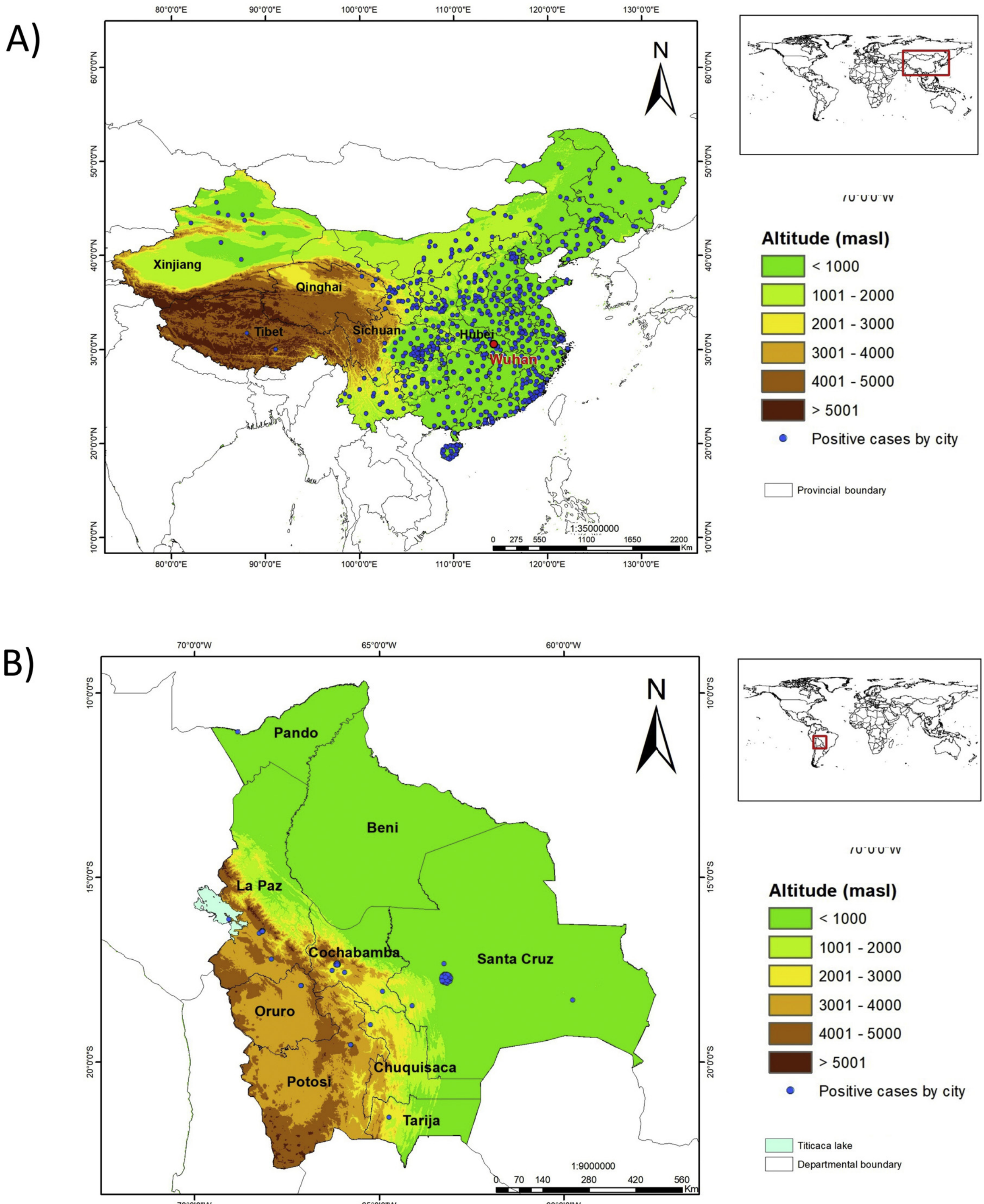

Fig. 1. A) Geographic and altitudinal distribution of COVID-19 pandemic in China. The blue dots represent COVID-19 positive cases. Geographic coordinates were retrieved from the real-time database elaborated by Xu et al. on March 30th (Xu et al., 2020). Altitude data were extracted from the digital elevation model of BIOCLIM. B) Geographic altitudinal distribution of COVID-19 pandemic in Bolivia. The blue dots represent COVID-19 positive cases. Geographic coordinates were included following the method used by Xu et al. on March 30th (Xu et al., 2020). Altitude data were extracted from the digital elevation model of BIOCLIM. This data is available at https://docs.google.com/spreadsheets/d/1sSK9-n0uoxzcRRQgQe2EYhDXb2zPea86gj1TjJnC9eo/edit?usp=sharing. In order to maintain this article up to date, the daily updated version of this graphic will be available in the following link until the end of the pandemic: https://altitudeclinic.com/blog/2020/04/covid-2-bolivia/.

cases reported since March 19) (Lu et al., 2020); (ii) in Bolivia (South America), one of the last countries affected by the pandemic, which has a third of its territory extended at high-altitude; and (iii) in Ecuador (South America), a country deeply affected by the pandemic, in which half of the population lives at high-altitude areas.

3. Results

3.1. Tibet

The Tibetan plateau, located on the north side of the Himalayas, has an average elevation of 4,000 m (Wu, 2001). Lhasa, the capital of Tibet,

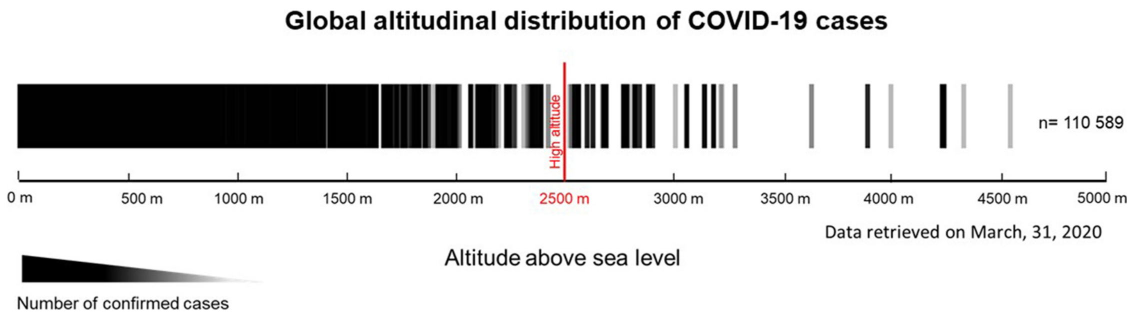

Fig. 2. Altitudinal distribution of COVID-19 pandemic in the World. The altitude for positive cases of COVID-19 was calculated using de digital elevation model of BIOCLIM and the geographic data from the real-time database elaborated by Xu et al. on March 31st (Xu et al., 2020).

is located at an elevation of 3,500 masl. The road distance between Lhasa and Wuhan (the center of the COVID-19 epidemic) is 3,503 km. However, Lhasa and Wuhan are also connected by train, bus, and by air, which indicates that tourist and commercial exchange between these cities may be considerable (Tseten, 2020). The impact of COVID-19 on the plateau region (of 9,000,000 inhabitants) has been drastically low compared to the rest of China (Lei et al., 2020). Indeed, only 134 confirmed cases were reported for the plateau region (Tibet, Qinghai and part of Sichuan) (Gelek, 2020; World-Health-Organization, 2020) (Fig. 1A). A representative cohort of 67 patients (only two imported cases) who were diagnosed with COVID-19 in Sichuan reveals that 54 % were completely asymptomatic (no cough, fever, or headache), and less than 10 % of the patients presented fever. Nevertheless, 10 % of the SARS-CoV-2 positive cohort developed severe medical condition, however, all of these patients fully recovered after treatment, resulting in no mortality. Moreover, 29 % of all the patients were at potential high-risk due to predisposition with chronic respiratory and/or cardiovascular disease at the time of COVID-19 diagnosis (Gelek, 2020; World-Health-Organization, 2020). Thus, it appears that both the pathogenesis of the SARS-CoV-2 virus and the general prevalence of infection in Tibet does not correspond to global trends.

3.2. Bolivia & Ecuador

The second analysis of the prevalence and impact of COVID-19 was performed for the central South American country Bolivia. La Paz, the administrative capital of Bolivia (2,706, 000 inhabitants) and the capital of the province of La Paz, is situated in a range of 2,400 to 4,000 masl, with a greater part of its metropolitan population located in the region of El Alto (at 4,150 masl, 922,598 inhabitants) (Instituto-Nacional-de-Estadística., 2018; Ministerio-de-Comunicación., 2017). Apart from the province of La Paz, the provinces of Oruro (at 3,735 masl; 538,200 inhabitants), Potosí (at 4,090 masl; 141,251 inhabitants), and Chuquisaca (2,810 masl, 300,000 inhabitants) are also part of the Bolivian high-altitude Andes (Instituto-Nacional-de-Estadística., 2018; Ministerio-de-Comunicación., 2017).

The first confirmed cases of COVID-19 in Bolivia were reported on March 10th, one in Oruro (a person returning from Italy), and a second in Santa Cruz (a person arriving from the United States). Four days later, on March 14th, seven new cases were confirmed in Oruro, and from that date until April 7th (26 days later), no new positive cases were confirmed. The first confirmed case of COVID-19 in La Paz was reported on March 19th, and to April 7th; (19 days later), there are a total of 36 confirmed new cases (8 imported, 28 local infections). Finally, only 8 positive cases of COVID-19 were detected in Potosí, and 1 in Chuquisaca, making a total of 54 cases in Bolivian provinces located at high-altitudes (Ministerio-de-Comunicación, 2020). Despite the fact that strict political measures were enacted across the country to restrict the movement of its population since the start of the pandemic (March 15th, restriction of access to Bolivia for travelers from the Schengen area, United Kingdom, Ireland and Iran; March 16th and 17th, restriction measures moderate circulation; March 21th, total quarantine; March 26th, state of sanitary emergency), the low rate of infections in Bolivia's high-altitude population is remarkable, and clearly does not follow the often exponential infection rates reported in many countries after an initial COVID-19 outbreak (World-Health-Organization, 2020) for this disease.

These data become more striking when compared to the rate of infection in Santa Cruz de la Sierra, the second largest and the most important province of Bolivia which is located at the Bolivian lowlands (400 masl; 1,686,375 inhabitants) (Instituto-Nacional-de-Estadística., 2018; Ministerio-de-Comunicación., 2017). Santa Cruz, which since the first registered case (March 10th) amassed a total of 100 positive Covid-19 cases until April 7th (Prensa-Latina, 2020). Furthermore, analyzing the Covid-19 pandemic in all Bolivian regions below 2,500 m until April 7th (40 cases distributed between Pando (110,436 inhabitants - 6 cases), Cochabamba (1,916,000 inhabitants - 33 cases), and Tarija (482,196 inhabitants - 1 case), there are a total of 140 infected patients (Ministerio-de-Comunicación, 2020). In conclusion it appears that Covid-19 infection rates at high-altitude regions in Bolivia are approximately three-fold lower than lowlands (Fig. 1B).

The Bolivian data are totally in line with data reported in Ecuador, a Latin American country that is severely affected by the pandemic. As of April 7th, four-fold less Covid-19 cases were in high-altitude areas of Ecuador (7,114,300 inhabitants) with only 722 cases, compared to 2943 cases in the coastal regions (8,328,300 inhabitants) (Gobierno-de-la-Republica-de-Ecuador, 2020).

3.3. A global view

World-wide about 120 towns and cities are located over 3,000 masl (Cohen and Small, 1998). Thus, to further support our hypothesis, we analyzed the real-time geographic data of the COVID-19 pandemic by Xu et al. (Xu et al., 2020). We combined these data with a digital elevation model (Hijmans et al., 2005) to illustrate the distribution of global positive COVID-19 cases in relation to altitude. As seen in Fig. 2, the number of COVID-19 cases show a distinct decrease when the affected population lives at an altitude of above 3,000 masl.

4. Discussion

Our epidemiological analysis of the Covid-19 pandemic clearly indicates a decrease of prevalence and impact of SARS-CoV-2 infection in populations living at altitude of above 3,000 masl. The reason for decreased severity of the global COVID-19 outbreak at high altitude could relate to both environmental and physiological factors.

Environmental factors may influence the virulence of SARS-CoV-2 at high-altitude. Indeed, a high-altitude environment is characterized by drastic changes in temperature between night and day, air dryness, and high levels of ultraviolet (UV) light radiation (United-States-Environmental-Protection-Agency, 2017). In particular UV light radiation A (UVA) and B (UVB) are well known to be capable of producing alterations in the molecular bonds of the DNA and RNA, and thus UV radiation at high-altitude may act as a natural sanitizer (Andrade, 2020; Zubieta-Calleja, 2020a; Zubieta-Calleja and Zubieta-DeUrioste, 2017). In relation to SARS-CoV-2, while complete disinfection cannot be achieved by UVA and UVB, these radiations should shorten the half-life of any given virus (Andrade, 2020; Zubieta-Calleja, 2020b). It is clear that, all together, these factors may dramatically reduce the "survival" capacity of the virus at high-altitude, and therefore its virulence. Finally, due to the lower density of air and greater distance between molecules at high-altitude, the size of the airborne virus inoculum must be smaller than at sea level.

Although the data of the present study suggest a strongly decreased pathogenicity of SARS-CoV-2 in high-altitude, there is yet no evidence of an underlying physiological mechanisms that could affect to severity of infection. However, there is a positive correlation between the infection rate of SARS-CoV-1 and ACE2 in pulmonary epithelial cells. Importantly both SARS-CoV-1 and SARS-CoV-2 bind to ACE2 (Lu et al., 2020; Rothan and Byrareddy, 2020; van Doremalen et al., 2020), and thus a putative decrease of ACE2 expression in pulmonary endothelia in high-altitude inhabitant could represent a physiological protective for the severe and often lethal pulmonary edema.

We conclude that the virulence of SARS-CoV-2 is reduced at high-altitude due to the physiological acclimatization of its inhabitants, and due to particular environmental characteristics. Furthermore, additional physiological acclimatization of high-altitude living associated with increased ventilation (Soliz et al., 2005), augmented arterial oxygen transport (Lundby et al., 2007), and higher tissue oxygenation (Kimakova et al., 2017), mainly (but not exclusively) mediated by erythropoietin could be explored for potential therapy (see Soliz et al., 2020, same issue RSPNB) of acute respiratory distress associated with COVID-19.

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