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MINI-REVIEW | *Hypoxia*

Geographic components of SARS-CoV-2 expansion: a hypothesis

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Joyce KE, Weaver SR, Lucas SJ. Geographic components of SARS-CoV-2 expansion: a hypothesis. *J Appl Physiol* 129: 257–262, 2020. First published July 23, 2020; doi:10.1152/japplphysiol.00362.2020.—The emergence of COVID-19 infection (caused by the SARS-CoV-2 virus) in Wuhan, China in the latter part of 2019 has, within a relatively short time, led to a global pandemic. Amidst the initial spread of SARS-CoV-2 across Asia, an epidemiologic trend emerged in relation to high altitude (HA) populations. Compared with the rest of Asia, SARS-CoV-2 exhibited attenuated rates of expansion with limited COVID-19 infection severity along the Tibetan plateau. These characteristics were soon evident in additional HA regions across Bolivia, central Ecuador, Nepal, Bhutan, and the Sichuan province of mainland China. This mini-review presents a discussion surrounding attributes of the HA environment, aspects of HA physiology, as well as, genetic variations among HA populations which may provide clues for this pattern of SARS-CoV-2 expansion and COVID-19 infection severity. Explanations are provided in the hypothetical, albeit relevant historical evidence is provided to create a foundation for future research.

COVID-19; high altitude; hypoxia; SARS-CoV-2

INTRODUCTION

The emergence of COVID-19 infection (caused by SARS-CoV-2) in Wuhan, China in the latter part of 2019 has, within a relatively short time, led to a global pandemic (13, 39, 81). Amidst the initial outbreak of COVID-19 and its expansion throughout mainland China, an epidemiologic trend emerged relative to high altitude (HA) populations. Lower transmission rates and reduced severity of COVID-19 infections were initially noted on the Qinghai-Tibetan plateau during the virus's rapid spread across Asia (49, 85). Growing evidence in support of similar trends have now been shown in Bolivia (1); Peru, Argentina, and Chile (24); HA regions of central Ecuador (1, 63); remote villages in Papua (78); the Sichuan province of mainland China (46, 91); Nepal and Bhutan (3); and Himalayan regions of India including Arunachal Pradesh and Ladakh (24). While it is acknowledged the pandemic is still in its early stages in some of these regions, the disproportionate spread of SARS-CoV-2 deserves further attention. The objective of this short review is to examine environmental and physiological factors associated with HA in regards to the disparate incidence and severity of COVID-19 infections between high- and low-altitude populations. The discussion is presented in the hypothetical, albeit historical evidence is provided with the intention of creating a foundation for future epidemiologic investigations of COVID-19 among HA populations.

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PHYSIOLOGICAL FACTORS

HA is associated with a reduced partial pressure of oxygen and concomitantly reduced arterial oxygenation. HA populations exhibit greater respiratory function evident in their superior ventilatory responses to hypoxia (71) and greater vital and total lung capacities (26). They display improved oxygen transport across the alveolar-arterial gradient and also utilize oxygen more effectively within cardiac tissue (44). Taken together, HA natives' ability to resist SARS-CoV-2 could be attributed to superior responses to hypoxemia with consequentially less strain on the heart in acute respiratory distress, which is critical if infection progresses (29, 81).

Hypoxic conditions have also been associated with down-regulation and suppression of several RNA and DNA viruses (e.g., adenovirus and influenza), which are often culprits of respiratory infections (45, 79). Mechanisms by which hypoxia inhibits viral replication can vary between viruses and require further investigation with regards to SARS-CoV-2. Nevertheless, adaptations associated with HA acclimatization have been linked to viral infection resistance and attributed to reductions in citric acid buildup that are believed to reduce viral synthesis in lung tissue (8). Similarly, associations between altitude-hypoxia and the restriction of *Mycobacterium tuberculosis* growth in whole blood and the augmentation of anti-mycobacterial cellular immunity (28) have been identified. Such effects are consistent with the HA-induced amplifications in cell-mediated immunity (increased PHA-blasts, lymphocyte migration index, and DNCB response) observed over 30 years earlier (17) and parallel the lower prevalence and reduced severity of tuberculosis (TB) infections at HA (62, 74).

SARS-CoV-2 may encounter similar immune challenges in hosts at HA which could explain the higher proportion of asymptomatic COVID-19 cases at HA (46, 49), as well as, the overall lower incidence and attenuated severity of symptomatic cases at HA (1, 63, 91). Genetic differences between the immunologic or inflammatory responses of lowlanders and highlanders (22, 90) may also be of interest given the apparent variability in immune and inflammatory responses to SARS-CoV-2 and the associated severity of COVID-19 infection (36, 39, 50, 65).

Whether the summation of these factors has significant benefits in regards to COVID-19 remains to be investigated fully; however, it is clear that HA populations exhibit unique physiological and health profiles that may have the potential for protection against the development and severity of COVID-19 infection. Investigations surrounding the immune and inflammatory responses to SARS-CoV-2 among lowlanders and HA natives are required. The recent emergence of dexamethasone as a successful treatment strategy for severe COVID-19 infection (38) aligns with its common use at HA, which targets problematic inflammation and capillary leak that accompany severe HA illness (e.g., HA cerebral edema) (43). Dexamethasone therefore presents a unique method for exploring HA-associated distinctions that may mitigate (or exacerbate) inflammatory responses to SARS-CoV-2.

ENVIRONMENTAL FACTORS

Numerous environmental characteristics associated with HA may also explain physiological findings and may be important in the future impact of COVID-19. Significant differences between highlanders and lowlanders are observed among the most commonly identified comorbidities (10) of COVID-19, with residence at higher elevation associated with lower incidence of cardiovascular disease and mortality (60), diabetes mellitus (83), obesity (84), and metabolic syndrome (51), which have all been linked to higher risk of severe COVID-19 infection and mortality (88). In contrast, hypertension appears to be higher in HA populations (2, 58, 61), although it is not possible to determine whether this puts these populations at a greater risk for COVID-19 infection, as there is still wide debate about whether the association between hypertension and COVID-19 embodies a causal relationship, or if it is simply indicative of the age and wider health status of those who are worst affected by COVID-19 (32, 70).

Pollution has also been associated with increased risk and severity of COVID-19 infections in high-pollution lowland areas (e.g., Lombardy, Italia, and New York, NY) (20, 96), and may relate to the emerging issue of hypercoagulability among COVID-19 patients (73). Reduced air pollution at HA (10, 31) is therefore of particular interest as is HA's possible mitigation of hypercoagulability via increases in fibrinolytic activity following two weeks of exposure (18).

Incidence patterns may also be mediated by differences in the levels of vitamin D, which are elevated at HA (47, 97). Indeed, the potential role of vitamin D in mortality among COVID-19 patients is being explored (33, 64). Ultraviolet (UV) radiation which increases alongside elevation should also be considered with respect to mortality in COVID-19, as increased radiation may help to inhibit viral replication (19).

CLIMATIC FACTORS

Similar to other zoonotic viruses (e.g., H1N1 influenza) (23, 52), factors such as temperature and humidity can influence SARS-CoV-2 infectivity (89) although the links appear to be quite dynamic (15). Lower temperatures and hypobaric-hypoxia at HA (above ~2,000 m) could, in part, explain the lower incidence of infections at HA, as they render the environment uninhabitable to non-human living vectors (e.g., *Aedes aegypti* mosquitos, flies, or other pests) (12, 53); however, recent evidence indicates that *Aedes* mosquitos do not pose a threat to SARS-CoV-2 transmission (86). Nevertheless, there has been evidence of an altitude "cut-off" for COVID-19 infections (~2,500 m) (1), which echoes the aforementioned insect line (12, 53). Thus, contributions from other insects whose inhabitancy is similarly thwarted at HA (e.g., flies) (75) should be considered, particularly, given their potentiation of fecal-oral transmission (67a) and the emerging evidence suggesting fecal-oral spread of SARS-CoV-2 (9, 57, 67, 87). Also of note are the lower incidences of viruses exhibiting fecal-oral transmission (e.g., gastrointestinal viruses) at HA (4), notwithstanding that fecal-oral transmission can also occur via several alternate pathways to the mouth (35).

Consistent and specific reporting of COVID-19 infections (e.g., residence vs. reporting facility altitude or geographic coordinates) will be important in evaluating links between HA-related climatic factors and SARS-CoV-2 transmission or COVID-19 infection severity and, ultimately, to help confirm or deny altitude protection against SARS-CoV-2.

ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2) INVOLVEMENT

The relationships between angiotensin-converting enzyme 2 (ACE2) expression and COVID-19 pathogenesis and mortality are undoubtedly complex with conflicting arguments within current research. Nonetheless, it has been suggested that changes in the level and activity of the ACE2 protein can alter COVID-19 outcomes (92). ACE2, a homolog of angiotensin-converting enzyme (ACE), is the primary infection route for SARS-CoV-2 (37, 95). Despite being crucial for viral entry, upregulation of ACE2 expression appears to confer protection against SARS-CoV-related lung injury (16, 41). Similarly, pro- vs anti-inflammatory imbalance (ACE-angiotensin II-ATI imbalance) associated with low ACE2 expression [e.g., with old age or in diabetes mellitus, DM (14)] has the potential to predispose patient's lungs to acute injury (34, 72) and could perpetuate the "cytokine storm" (76) observed in COVID-19 (56) that is known to confer poor outcomes, particularly, among the elderly and those with DM (94).

Acute upregulation of ACE2 appears possible with hypoxic exposures (21, 93). Likewise, prevention of ACE2 downregulation seems plausible (59). By limiting SARS-CoV-2-induced ACE2 depletion that ensues following receptor binding (92), ACE2 upregulation may thereby attenuate associated pulmonary inflammation and lung damage (41, 77). Clinical recommendations for the continuance of ACE inhibitor and angiotensin receptor blocker (ARB) therapies (30), which both upregulate ACE2, are consistent with ACE2-upregulation being beneficial. Whether hypoxia directly or indirectly translates into a definitive physiological advantage over SARS-CoV-2 via ACE2 involvement remains unclear. Careful evaluations of

pulmonary ACE2 in humans in response to various durations and intensities of hypoxic exposures would be helpful in determining the relevance of ACE2 in this context.

GENETIC FACTORS

Genomic ancestry supports genetic links between the anti-COVID-19 display among HA populations. In HA regions such as Ladakh, Arunachal Pradesh, Manipur, and Mizoram, the Tibeto-Burman genetic composition predominates and COVID-19 infections have been limited (24). Similarly, higher fractions of Paleo-Eskimo ancestry in HA regions of Peru and Mexico have been accompanied by considerably lower death rates (24). Together with the genetic differences known to exist between HA populations (Andean vs. Tibetan) (5), it is conceivable that evolutionary components may also exist with regards to anti-COVID-19 displays. Analyses of existing genetic data from various HA populations would be useful to further investigate this.

Population and ethnic differences in a number of genes related to ACE2 have also been suggested as having a potential role in COVID-19. Support can be provided by the differences in relative binding affinities for SARS-CoV-2 between ACE2 allelic variants (40), as well as in gene-variant dependent effects on viral internalization processes that appear to influence susceptibility to SARS-CoV-2 (7). Ethnic variations in the expression of ACE2 (11) have also been highlighted. Genetic variability in ACE2 among HA populations may help to modulate resistance and susceptibility to viral infection; however, investigations into the dynamics of pulmonary ACE2 expression across a range of genetic profiles in response to SARS-CoV-2 are required to better understand the significance of ACE2 genetic variation as it relates to COVID-19 infection.

Relative frequency of the ACE gene's deletion allele (D; vs. the insertion allele, I) parallels reductions in ACE2 expression and has been implicated in the pathogenesis of acute respiratory distress syndrome (ARDS) (55) and SARS-CoV-1 (48). Consistent with this are the higher numbers of COVID-19 cases among black populations (27, 66), who exhibit relatively low I allelic frequency (68), as well as the lower incidence and severity of infections among HA populations, who exhibit high I allelic frequency (82). In contrast, Delanghe and colleagues suggest that a higher I allele frequency may actually be detrimental to COVID-19 outcomes within European populations (25). These conflicting epidemiologic data emphasize the complexity of the relationships between COVID-19 and ACE genotype or ACE2. Nevertheless, given the potential impact of ACE polymorphisms on resultant ACE2 and COVID-19 outcomes, it is clear the duo warrant further exploration.

Alternative gene variants also differ between ethnic groups (42), such as angiotensin II type 1 receptor (or the AGTR1 gene), and thus deserve attention; notwithstanding that SARS-CoV-2 infection is distinctly different from existing pathophysiological variability between AGTR1 gene variants (54). Genes related to vascular inflammation (69) may also be worthy of investigation, although a complex relationship between components of the vasoregulatory axis and SARS-CoV-2 is likely.

LIMITATIONS AND CONSIDERATIONS

We acknowledge there are a number of limitations to this perspective. Underreporting in HA regions is possible, although unlikely for symptomatic infections as low notifications for other severe respiratory infections have accurately reflected actual cases (80). Disparities in tracking and tracing capacities between high- and low-altitude regions may allow the higher proportion of asymptomatic cases at HA (46) to go undetected; however, this would further support the argument for reduced case severity at HA. Actions that aid testing and reporting efforts in HA regions could improve comparisons (high vs. low altitude) related to COVID-19 infections.

It is also acknowledged that HA can exacerbate certain respiratory infections (4) and may be contraindicated in those with severe existing disease (54). Under no circumstances is the presented evidence intended to justify HA exposure for prophylactic use or treatment against COVID-19.

CONCLUSIONS

The transmission of SARS-CoV-2 and severity of COVID-19 infections may embody a clinal pattern specifically related to HA with subsequent physiological advantages over COVID-19 being possible among HA populations. Future research could benefit from utilizing existing genetic and physiological data pertaining to HA populations to evaluate presented theories related to the prevalence of SARS-CoV-2 and severity of COVID-19 among HA populations.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

K.E.J. and S.R.W. conceived and designed research; K.E.J. and S.R.W. drafted manuscript; K.E.J., S.R.W., and S.J.E.L. edited and revised manuscript; K.E.J., S.R.W., and S.J.E.L. approved final version of manuscript.

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