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Response by Bhatnagar to Letter Regarding Article, "Environmental Determinants of Cardiovascular Disease"

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In Response

Dr Calderon-Gerstein raises interesting issues related to the cardiovascular effects of high altitude. These effects could be categorized into (1) acute or chronic effects in lowlanders moving to high altitude, (2) partial adaptation to high altitude in populations of recent altitude ancestry (eg, Andean natives), and (3) long-term adaptations in populations of old altitude ancestry (eg, Sherpa and Tibetans). Some of these effects are similar, whereas others are not. Although, in lowlanders, moving from low to high altitude triggers hypoxia-related changes, populations with long altitude ancestry have adapted to low oxygen levels and other environmental features unique to high altitude and, therefore, are relatively insensitive to hypoxia.[1] Dr Calderon-Gerstein correctly points out that individuals with recent altitude ancestry, such as the Andean natives, develop right, not left, ventricular hypertrophy. In newborns at sea level, right ventricular hypertrophy decreases promptly after birth, but it persists throughout life in Andean children living at 4540 m.[2] Similarly, as discussed later in the review,[3] when lowlanders ascend to high altitude, there is an increase in pulmonary artery pressure and pressure load on the right ventricle. However, increased right ventricular afterloads lead to a decrease in left ventricular (LV) filling pressure and delayed LV untwist[4] and decreased LV volumes.[5] In adapted populations, such as the Tibetans, right ventricular abnormalities are less common than among Han immigrants to the area or patients with chronic mountain sickness.[6] Moreover, there is evidence to suggest that despite a lower risk of coronary heart disease, Tibetans display ECG characteristics consistent with LV hypertrophy.[7]

A similar distinction can be made about leptin levels. Hypoxia stimulates the hypoxia-induced factor (HIF)-α–dependent expression of the leptin gene, but conflicting effects of hypoxia on leptin have been reported in the literature.[8] The transient increase in leptin reported by some investigators[9–11] is associated with lowlanders moving to a higher altitude. Similarly, a transient decrease in ghrelin levels was observed in individual moving from low to high altitude.[12] In contrast, individuals acclimatized to high altitude, as discussed in the review, show a decrease in leptin levels,[13,14] and leptin levels in mountain dwellers show an inverse relationship with altitude.[15,16] This inverse relationship persisted even after adjusting for age, body-mass index, physical activity, blood pressure, and alcohol.[16] Such divergent

Disclosures

None.

effects of altitude may be because of the stimulation of HIF-α by hypoxia in nonadapted, but not in adapted, individuals.[1] Finally, even though the pioneering work of Arias-Stella et al[2] shows higher elaboration of coronary microcirculation in Andean natives, it is unclear whether other populations show similar adaptations. High-altitude residents in general have normal or even decreased coronary blood flow.[17] Indeed, skeletal muscle angiogenesis and the levels of vascular endothelial growth factor were found not to be different in Aymara high-altitude natives compared with sea-level residents.[18] Therefore, even though some Andean natives have more elaborate coronary microcirculation, the relative contribution of this adaptation to lower rates of cardiovascular disease in this and other high-altitude populations, vis-à-vis other physiological differences (eg, in lipid metabolism, blood pressure regulation, or other metabolic processes), remains unclear and deserves further study.

References

1. Petousi N, Croft QP, Cavalleri GL, Cheng HY, Formenti F, Ishida K, Lunn D, McCormack M, Shianna KV, Talbot NP, Ratcliffe PJ, Robbins PA. Tibetans living at sea level have a hyporesponsive hypoxia-inducible factor system and blunted physiological responses to hypoxia. J Appl Physiol. 2014; 116:893–904. DOI: 10.1152/japplphysiol.00535.2013 [PubMed: 24030663]
2. Penaloza D, Arias-Stella J. The heart and pulmonary circulation at high altitudes: healthy highlanders and chronic mountain sickness. Circulation. 2007; 115:1132–1146. DOI: 10.1161/CIRCULATIONAHA.106.624544 [PubMed: 17339571]
3. Bhatnagar A. Environmental determinants of cardiovascular disease. Circ Res. 2017; 121:162–180. DOI: 10.1161/CIRCRESAHA.117.306458 [PubMed: 28684622]
4. Maufrais, C., Rupp, T., Bouzat, P., Doucende, G., Verges, S., Nottin, S., Walther, G. Heart mechanics at high altitude: 6 days on the top of Europe [published online ahead of print December 22, 2016]. Eur Heart J Cardiovasc Imaging. doi: https://doi.org/10.1093/ehjci/jew286
5. Dedobbeleer C, Hadefi A, Pichon A, Villafuerte F, Naeije R, Unger P. Left ventricular adaptation to high altitude: speckle tracking echocardiography in lowlanders, healthy highlanders and highlanders with chronic mountain sickness. Int J Cardiovasc Imaging. 2015; 31:743–752. DOI: 10.1007/s10554-015-0614-1 [PubMed: 25665685]
6. Halperin BD, Sun S, Zhuang J, Droma T, Moore LG. ECG observations in Tibetan and Han residents of Lhasa. J Electrocardiol. 1998; 31:237–243. [PubMed: 9682900]
7. Aryal N, Weatherall M, Bhatta YK, Mann S. Electrocardiography in people living at high altitude of Nepal. Heart Asia. 2017; 9:48–53. DOI: 10.1136/heartasia-2016-010838 [PubMed: 28243317]
8. Debevec T. Hypoxia-related hormonal appetite modulation in humans during rest and exercise: mini review. Front Physiol. 2017; 8:366.doi: 10.3389/fphys.2017.00366 [PubMed: 28611686]
9. Shukla V, Singh SN, Vats P, Singh VK, Singh SB, Banerjee PK. Ghrelin and leptin levels of sojourners and acclimatized lowlanders at high altitude. Nutr Neurosci. 2005; 8:161–165. DOI: 10.1080/10284150500132823 [PubMed: 16117183]
10. Lippl FJ, Neubauer S, Schipfer S, Lichter N, Tufman A, Otto B, Fischer R. Hypobaric hypoxia causes body weight reduction in obese subjects. Obesity. 2010; 18:675–681. DOI: 10.1038/oby.2009.509 [PubMed: 20134417]
11. Tschöp M, Strasburger CJ, Töpfer M, Hautmann H, Riepl R, Fischer R, Hartmann G, Morrison K, Appenzeller M, Hildebrandt W, Biollaz J, Bärtsch P. Influence of hypobaric hypoxia on leptin levels in men. Int J Obes Relat Metab Disord. 2000; 24(suppl 2):S151. [PubMed: 10997640]
12. Riepl RL, Fischer R, Hautmann H, Hartmann G, Müller TD, Tschöp M, Toepfer M, Otto B. Influence of acute exposure to high altitude on basal and postprandial plasma levels of gastroenteropancreatic peptides. PLoS One. 2012; 7:e44445.doi: 10.1371/journal.pone.0044445 [PubMed: 22970220]

13. Zaccaria M, Ermolao A, Bonvicini P, Travain G, Varnier M. Decreased serum leptin levels during prolonged high altitude exposure. Eur J Appl Physiol. 2004; 92:249–253. DOI: 10.1007/s00421-004-1070-0 [PubMed: 15083363]

14. Vats P, Singh SN, Shyam R, Singh VK, Singh SB, Banerjee PK, Selvamurthy W. Leptin may not be responsible for high altitude anorexia. High Alt Med Biol. 2004; 5:90–92. DOI: 10.1089/152702904322963753 [PubMed: 15072723]

15. Woolcott OO, Castillo OA, Torres J, Damas L, Florentini E. Serum leptin levels in dwellers from high altitude lands. High Alt Med Biol. 2002; 3:245–246. DOI: 10.1089/15270290260131975 [PubMed: 12162867]

16. Cabrera de Leon A, Gonzalez DA, Mendez LI, Aguirre-Jaime A, del Cristo Rodriguez Perez M, Coello SD, Trujillo IC. Leptin and altitude in the cardiovascular diseases. Obes Res. 2004; 12:1492–1498. [PubMed: 15483214]

17. Moret P, Covarrubias E, Coudert J, Duchosal F. Cardiocirculatory adaptation to chronic hypoxia: comparative study of coronary flow, myocardial oxygen consumption and efficiency between sea level and high altitude residents. Acta Cardiol. 1972; 27:283–305. [PubMed: 4537818]

18. Lundby C, Pilegaard H, Andersen JL, van Hall G, Sander M, Calbet JA. Acclimatization to 4100 m does not change capillary density or mRNA expression of potential angiogenesis regulatory factors in human skeletal muscle. J Exp Biol. 2004; 207:3865–3871. DOI: 10.1242/jeb.01225 [PubMed: 15472017]