The Effect of Hypoxia on Cardiovascular Disease: Friend or Foe?

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Abstract

Savla, Jainy J., Benjamin D. Levine, and Hesham A. Sadek. The effect of hypoxia on cardiovascular disease: Friend or foe? *High Alt Med Biol.* 19:124–130, 2018.—Over 140 million people reside at altitudes exceeding 2500 m across the world, resulting in exposure to atmospheric (hypobaric) hypoxia. Whether this chronic exposure is beneficial or detrimental to the cardiovascular system, however, is uncertain. On one hand, multiple studies have suggested a protective effect of living at moderate and high altitudes for cardiovascular risk factors and cardiovascular disease (CVD) events. Conversely, residence at high altitude comes at the tradeoff of developing diseases such as chronic mountain sickness and high-altitude pulmonary hypertension and worsens outcomes for diseases such as chronic obstructive pulmonary disease. Interestingly, recently published data show a potential role for severe hypoxia as a unique and unexpected therapy after myocardial infarction. In this review, we will discuss the current literature evaluating the effects of altitude exposure and the accompanying hypoxia on health and the potential therapeutic applications of hypoxia on CVD.

Keywords: altitude; cardiovascular disease; hypoxia

ACROSS THE WORLD, many diverse populations have been residing at altitudes exceeding 2500 m for hundreds and in some regions, perhaps thousands of years (Moore et al., 1998). Despite this long history, the effects of moderate- and high-altitude exposure on human health remain uncertain. Numerous epidemiologic, physiologic, and animal studies have been published evaluating the positive and negative effects of altitude on cardiovascular disease (CVD). Much of this published literature is conflicting on the specific role of altitude on the development of CVD or related conditions. Most importantly, the impact of exposure to atmospheric hypoxia, which accompanies living at altitude, is unclear and extremely difficult to isolate from the genetic and environmental factors that are well known to influence CVD among different populations. In this review, we will discuss the physiologic changes which occur with chronic altitude exposure, evaluate the current literature surrounding the positive and negative consequences of living at moderate altitude and examine the potential therapeutic applications of hypoxia. The cardiovascular response to altitude, both acute and chronic, has been reviewed recently in detail (Baggish et al., 2014; Levine, 2015) and thus will be covered only briefly in this study.

Cardiovascular Physiologic Changes After Altitude Exposure

With increases in altitude, there are decreases in barometric pressure. At moderate and high levels of altitude (Bartsch et al., 2008), this results in a reduction in the partial pressure of oxygen and ultimately leads to alveolar hypoxia. There are a number of well-defined changes that occur in the cardiovascular system after acute and chronic acclimatization to altitude. It should be noted that many of these studies were performed in healthy controls, the majority of which were healthy young men; thus, the data base regarding the effect of altitude on women, the elderly, or patients with systemic diseases is remarkably limited. With acute exposure, the stroke volume increases. After a few days, that initial increase abates and the stroke volume falls to levels that are lower than sea level (Richardson et al., 1967; Vogel et al., 1967; Hoon et al., 1977). Heart rate is also increased with altitude exposure and remains elevated with sustained exposure (Baggish et al., 2014; Siebenmann and Lundby, 2015). The degree of elevation in the heart rate correlates to the amount of elevation from sea level. Even with exposure to severe hypoxia, left ventricular contractility is preserved (Buch et al., 1980; Fowles

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and Hultgren, 1983; Reeves et al., 1987; Suarez et al., 1987). However, there are reductions in left ventricular end diastolic volume observed with sustained hypoxia. This finding is mostly attributed to a reduction in plasma volume, although pulmonary hypertension and ventricular function likely play some role depending on the degree of both absolute hypoxia and hypoxic pulmonary vasoconstriction (Alexander et al., 1967; Fowles and Hultgren, 1983; Suarez et al., 1987; Hirata et al., 1991). In addition, exercise capacity is reduced with exposure to altitude and the pulmonary artery pressure increases abruptly with exercise even after acclimatization. In terms of coronary blood flow, hypoxia results in increased levels of coronary blood flow to accommodate the reduction in arterial O₂ content, although ultimate values in the chronic state can vary between the right and left coronary arteries and depend on both the supply side (restoration of arterial oxygen content from acclimatization) and the demand side (myocardial oxygen demands based on HR and ventricular loading conditions) (Moret et al., 1972; Grover et al., 1976). Coronary flow reserve is preserved in healthy individuals at altitude, but decreases in those with known coronary artery disease (CAD) during exercise (Wyss et al., 2003; Arbab-Zadeh et al., 2009).

Multiple additional physiologic changes occur during sustained exposure to hypoxia that impact the cardiovascular system. Persistent exposure to altitude results in sympathetic hyperactivity (Hansen and Sander, 2003; Lundby et al., 2018), which leads to downregulation of beta receptors, the impact of which is unclear (Bristow et al., 1982; Kacimi et al., 1992). There are also changes in hemoglobin-O₂ affinity and hypoxia-mediated erythropoietin production, which stimulate red blood cell production. Although the red cell mass increases with time at altitude, the reduction in plasma volume that occurs with exposure to moderate and high altitudes persists resulting in a relative preservation of total blood volume (Myhre et al., 1970; Jain et al., 1980).

On a transcriptional level, many of these responses are mediated by the hypoxia-inducible factor (HIF) family of transcription factors binding to hypoxia-response elements located near genes that control these changes. The HIFs have been linked to a number of adaptive responses to hypoxia, including erythropoiesis (Semenza and Wang, 1992). In the Tibetan population, the role of variants in the HIF2 α gene on adaptation to chronic hypoxia have been studied by a number of groups with links to lower hematocrit and lower pulmonary vasoconstriction response (Groves et al., 1993; Beall, 2000), although the influence of plasma volume regulation in this response has largely been ignored and may be important (Dunn et al., 2007). In addition to the HIF family, the expression patterns of over 40 genes are altered by hypoxia, including vascular endothelial-growth factor- α , pyruvate dehydrogenase kinase, isoform 1, inducible nitric oxide synthase, and prostaglandin I₂ synthase. While some of these genes are known to work in specific pathways, the function of many of these genes is not known. In addition, genome wide association studies have identified variants in a number of genes that may facilitate adaptation to high altitude (Zimmerman et al., 1991; Semenza and Wang, 1992; Melillo et al., 1995; Tudor et al., 1995; Lau et al., 1997; Zdobornyj et al., 2009; Simonson et al., 2010; Hu et al., 2017). This may be of relevance especially in light of the known negative feed-back loop, which results in downregulation of HIF1 α mRNA with prolonged hypoxia exposure (Ginouves et al., 2008).

With chronic exposure to altitude and hypoxia, there are moderate elevations in pulmonary artery pressure resulting from vascular remodeling. One of the key responses of vascular remodeling is muscularization of the distal vessels. The relationship between altitude and lung disease is further explored by Grissom and Jones in this issue. In terms of the systemic circulation, there are elevations in systemic arterial pressure and vascular resistance (Klausen, 1966; Vogel et al., 1967, 1974; Sharma et al., 1977; Bender et al., 1988; Wolfel et al., 1991, 1998; Savard et al., 1995). While these changes occur shortly after exposure to hypoxia, these changes do not seem to persist after several months (Marticorena et al., 1969; Sharma et al., 1978).

Is Residence at Altitude Beneficial?

The initial data evaluating the effects of altitude are derived from epidemiologic studies. While these studies compared high-altitude populations versus low-altitude populations, the published results are inconsistent across a variety of diseases. In terms of CVD, several studies show a reduced risk of CVD with increases in altitude, while multiple studies conclude the opposite result (Mortimer et al., 1977; Temte, 1996; al Tahan et al., 1998; Baibas et al., 2005; Al-Huthi et al., 2006). Similar conflicting findings are seen for studies evaluating risk factors for CVD such as hypertension and hyperlipidemia (de Mendoza et al., 1979; Mirrakhimov et al., 1985; Sharma, 1990; Khalid et al., 1994; Wolfel et al., 1994; al Tahan et al., 1998; Pasini et al., 1999; Dominguez Coello et al., 2000; Fiori et al., 2000; Jefferson et al., 2002). The majority of these conflicting findings result from confounding factors, which were not adequately addressed in the study design and analysis. In much of this literature, the comparison groups are heterogeneous in terms of ethnicity and traditional CVD risk factors. Additional factors that could affect assessment of the outcome such as access to healthcare, migration, exposure to relatively low altitudes and total altitude exposure over a lifetime were not assessed in many of these studies.

In 2009, Faeh et al. utilized the Swiss National Cohort Study Group to evaluate the effect of altitude on CVD. This study addresses many of the limitations of previous studies as the Swiss population is more homogenous and has access to universal healthcare, minimizing the role of healthcare utilization on CVD. In addition, this cohort has information on the location of birth and the place of residence to better estimate the amount of exposure to altitude. Using data from ~1.64 million German Swiss residents, they show a beneficial effect of high altitude on CAD and stroke. Individuals who were born at high altitude also have an independent protective effect for CAD (Faeh et al., 2009).

The beneficial effects of high altitude on heart disease are consistently seen in other more recently published studies. Similar to Faeh et al. (2009) a study evaluating the US population examines the relationship between CVD and altitude. Using a variety of data sources, including the National Center for Health Statistics, the National Elevation Dataset, and the U.S. Census Estimates, they demonstrate a beneficial dose-response relationship between altitude and CVD. Their analysis adjusts for sociodemographic factors, migration, exposure to solar radiation, and cumulative exposure to smoking, addressing the weaknesses of previously published studies (Ezzati et al., 2012). A second study of heart disease in the United States from 2008 through 2011 uses data from 11 states

considered to be low-altitude states and 5 states considered to be high-altitude states. Consistent with the recently published studies, they show that the incidence of heart diseases is lower in the high-altitude states (Hart, 2015). A follow-up study from the Swiss National Cohort evaluates the effects of environmental factors on cardiovascular mortality. Using data from 4.2 million individuals, they found that mortality from CVD decreases linearly with increases in altitude. While this association can be attributed to environmental factors such as low amounts of pollution or increased physical activity, the positive effect of altitude remains after adjusting for all other environmental factors (Faeh et al., 2016). Among dialysis patients, lower rates of myocardial infarction, stroke, and cardiovascular death are seen at higher altitudes (Winkelmayer et al., 2012).

The benefits of altitude exposure are described with several other diseases with close linkage to cardiovascular disorders. A cross sectional study from the United States shows that adults living at altitudes of 1500–3500 m are less likely to have diabetes and obesity compared with adults living at elevations of 0–499 m. After adjusting for factors such as age, physical activity, and obesity, the association between diabetes and altitude persisted (Woolcott et al., 2014). In terms of hyperlipidemia, a study of an Omani Arab population residing at high altitude demonstrates elevated high density lipoprotein cholesterol (HDL-C) levels, while a cross-sectional Turkish study shows that dyslipidemia is negatively associated with altitude (Bayram et al., 2014; Al Riyami et al., 2015). This effect is thought to be mediated through HIF1 in reducing cholesterol synthesis by 3-hydroxy-3-methylglutaryl-CoA reductase (Nguyen et al., 2007). However, these studies are limited by many of the confounders described above. The effect of altitude is also seen on obesity and metabolic syndrome. Among overweight service members in the U.S. Army and Air Force, those stationed at high-altitude locations have a lower incidence of obesity (Voss et al., 2014). In a comparison of high and low populations in Peru, individuals residing in high-altitude regions are less likely to have metabolic syndrome, elevated high-sensitivity C-reactive protein, and insulin resistance (Benziger et al., 2015). The interpretation of these studies is limited by the small sample size and presence of residual confounding. When looking at less common cardiac conditions, improved survival is seen in patients living above 2000 feet after heart transplant (Wozniak et al., 2012), while in a small series of patients undergoing surgical repair of atrial septal defects or ventricular septal defects, patients at high altitude have lower troponin I values and change in brain natriuretic peptide after surgery (Hu et al., 2014). While these studies highlight an interesting potential benefit to altitude exposure on postsurgical outcomes, these results must be interpreted with caution due to the small sample sizes and the limitations inherent to the datasets queried.

The Tradeoffs

The lower incidences of obesity, diabetes, hyperlipidemia, and CAD for populations that live at high altitudes come at a price. A well described possible consequence of chronic altitude exposure is chronic mountain sickness. Chronic mountain sickness is characterized by erythrocytosis, neurologic symptoms, pulmonary hypertension, and cor pulmonale (Villafuerte, 2015).

It is proposed that chronic exposure to high altitude is also associated with systemic hypertension. However, the

data supporting this association is murky with many limitations. In a meta-analysis of cross-sectional studies from Tibet, a 2% increase in prevalence of hypertension is seen with every 100 m increase in altitude (Mingji et al., 2015). A second meta-analysis finds similar results in the Tibetan populations (Aryal et al., 2016). The impact of these studies is difficult to take at face value due to the limited available data in this field, the inclusion of cross-sectional studies, the lack of patient-level data, and variation in patient characteristics between the studies included. In a study from Japan, elevated diastolic blood pressure is seen in high-altitude populations (Otsuka et al., 2005). This finding is difficult to interpret as they compared a low-altitude population from a single community in Japan to a high-altitude community from Ladakh. Recent studies from China show an increased risk of hypertension in high-altitude populations. However, these individuals also have multiple comorbidities that increase the risk for developing hypertension such as active smoking, obesity, and poor lifestyle (Shen et al., 2017; Yue et al., 2017). In contrast to these findings, some studies have found a null or beneficial effect of altitude on hypertension. A study evaluating trekkers with and without hypertension shows that both systolic and diastolic blood pressures remain stable with exposure to high altitude. However, there are participants in both groups that experienced severe, asymptomatic hypertension with an unclear consequence (Keyes et al., 2017). A major limitation of this study is that blood pressure measurements began once the participants had reached 2860 m with no sea level blood pressures available for comparison.

An evaluation of urban, semiurban, and rural populations from Peru finds a lower incidence of hypertension among those living at high altitudes. The high-altitude population studied also has a lower incidence of obesity, a known risk factor for developing hypertension, introducing confounding into the interpretation of the results. In addition, other factors that may influence obesity and hypertension were not evaluated thoroughly in this study such as lifestyle factors and access to healthcare (Bernabe-Ortiz et al., 2017). While many more studies exist evaluating the link between hypertension and exposure to chronic hypoxia, these studies highlight the controversy in proclaiming an association between these entities and provide an area for future research.

In terms of high-altitude pulmonary hypertension, little information is available on the prevalence of this disease. Some of the difficulty in studying this disease arises from the overlap in symptoms between high-altitude pulmonary hypertension and other lung diseases and the requirement of invasive hemodynamics for definitive diagnosis. A more in-depth review of the relationship between altitude exposure and lung disease can be found in the review by Grissom and Jones in this issue. The negative effects of altitude are also seen in several other disease conditions. In terms of individuals with known CAD, exposure to hypoxia alone is not sufficient to cause ischemia, but diseased segments of the coronary artery fail to exhibit hypoxia-induced vasodilation (Karliner et al., 1985; Malconian et al., 1990; Arbab-Zadeh et al., 2009). Additional research in this area is needed to clarify the safety of exposure to prolonged hypoxia in these patients.

In animal studies, rats exposed to chronic hypoxia exhibit increased plasma and hepatic triglycerides (Siques et al., 2014). Elevated triglycerides are also seen in a study of army men exposed to chronic intermittent hypoxia (Brito et al., 2007). In high-elevation populations in Peru, higher body

mass index and lower pulmonary function are associated with lower resting daytime oxyhemoglobin saturation. Lower resting daytime oxyhemoglobin is associated with higher odds of having metabolic syndrome, insulin resistance, higher hemoglobin A1c levels, and higher high-sensitivity C-reactive protein levels (Miele et al., 2016). In addition, high-altitude populations are at risk for developing high-altitude renal syndrome, which is characterized by polycythemia, hyperuricemia, systemic hypertension, and microalbuminuria with preserved glomerular filtration rate (Hurtado et al., 2012). Decreased glomerular filtration rate is seen with chronic intermittent altitude exposure (Brito et al., 2007).

Hypoxia as a Potential Therapeutic

Animal studies demonstrate a favorable effect of exposure to hypoxia on CVD. In contrast to the adult mammalian heart, which is one of the least proliferative organs, some vertebrate species, such as zebrafish, have a remarkable capacity for heart regeneration (Poss et al., 2002). This regenerative capacity is largely driven by continuously cycling cardiomyocytes rather than cell cycle-arrested cardiomyocytes, which populate the adult mammalian heart. In addition, zebrafish and adult mammals have significant physiologic differences. The zebrafish heart is exposed to a hypoxic environment due to the mixing of arterial and venous blood (Nikinmaa, 2002). Studies of the neonatal mammalian heart establish a short window of time immediately after birth, in which significant cardiomyocyte proliferation can occur even after injury. Cardiac injury that occurs after this window has passed results in fibrosis and scar formation (Porrello et al., 2011, 2013; Xin et al., 2013; Aurora et al., 2014; Bryant et al., 2015; Darehzereshki et al., 2015; Mahmoud et al., 2015; O'Meara et al., 2015; Polizzotti et al., 2015; Xiao et al., 2017).

In adult mice, exposure to chronic hypoxia equivalent to the summit of Mount Everest leads to decreased mitochondrial reactive oxygen species production and reduced oxidative DNA damage. It also induces hyperplastic growth of the heart by evidence of increased cell cycle activity and increased total cardiomyocyte number. After myocardial infarction, adult mice exposed to hypoxia show significant myocardial recovery with increased coronary collaterals, improvement in ejection fraction, and reduced scar formation. Several contributing factors likely underlie this improvement. Chronic hypoxia alters mitochondrial metabolism with reduction of enzymes involved in the Krebs cycle and fatty acid β -oxidation. As previously described, HIF1 α expression is stabilized with chronic hypoxia. In addition, a number of metabolic pathways are significantly dysregulated in the hypoxia group (Nakada et al., 2017). While the data from this study demonstrates a potential role for hypoxia as a therapeutic strategy for cardiac recovery after myocardial infarction, further studies are needed to gain a better understanding of the mechanisms driving improvement in cardiac function.

In addition, there are multiple barriers to translating these findings to humans who have sustained a previous myocardial infarction. Although altitude-like conditions can be simulated in a variety of ways, it has only been applied in human trials as an intermittent condition. Developing a protocol or device for chronic exposure that can be applied to patients after myocardial infarction for weeks at a time is a challenge that will need to be surmounted to make this an accessible and viable therapy. It is also not clear that the benefits of hypoxia therapy

in this patient population will outweigh the possible adverse effects that come with the physiologic changes that we outlined earlier in this review. Further work in this field is needed to develop a feasible treatment strategy that harnesses the beneficial effects associated with chronic hypoxia for individuals with CAD.

Conclusions

A number of studies have been published evaluating the impact of living at altitude on the development of CVD and related diseases such as dyslipidemia, obesity, and hypertension. Many of the initial studies in this field have conflicting findings driven by significant confounding. More recent studies that have addressed many of these confounders have demonstrated the beneficial effects of hypoxia on CVD and risk factors for CVD. However, this benefit comes at the risk of developing several conditions that are potentially associated with acute and chronic exposure to high altitude such as high-altitude pulmonary edema, pulmonary hypertension with possible heart failure, and renal disease. Interestingly, animal data have demonstrated the significant positive effects of exposure to extreme hypoxia after myocardial infarction. More research is needed to define the mechanism driving the positive effects of hypoxia that it can potentially be applied to larger populations while mitigating the negative effects.

Author Disclosure Statement

No competing financial interests exist.

References

- Al-Huthi MA, Raja'a YA, Al-Noami M, and Abdul Rahman AR. (2006). Prevalence of coronary risk factors, clinical presentation, and complications in acute coronary syndrome patients living at high vs low altitudes in Yemen. *MedGenMed* 8:28.
- Al Riyami NB, Banerjee Y, Al-Waili K, Rizvi SG, Al-Yahyaee S, Hassan MO, Albarwani S, Al-Rasadi K, and Bayoumi RA. (2015). The effect of residing altitude on levels of high-density lipoprotein cholesterol: A pilot study from the Omani Arab population. *Angiology* 66:568–573.
- al Tahan A, Buchur J, el Khwsky F, Oggunniyi A, al-Rajeh S, Larbi E, Daif A, and Bamgboye E. (1998). Risk factors of stroke at high and low altitude areas in Saudi Arabia. *Arch Med Res* 29:173–177.
- Alexander JK, Hartley LH, Modelski M, and Grover RF. (1967). Reduction of stroke volume during exercise in man following ascent to 3,100 m altitude. *J Appl Physiol* 23:849–858.
- Arbab-Zadeh A, Levine BD, Trost JC, Lange RA, Keeley EC, Hillis LD, and Cigarroa JE. (2009). The effect of acute hypoxemia on coronary arterial dimensions in patients with coronary artery disease. *Cardiology* 113:149–154.
- Aryal N, Weatherall M, Bhatta YK, and Mann S. (2016). Blood pressure and hypertension in adults permanently living at high altitude: A systematic review and meta-analysis. *High Alt Med Biol* 17:185–193.
- Aurora AB, Porrello ER, Tan W, Mahmoud AI, Hill JA, Bassel-Duby R, Sadek HA, and Olson EN. (2014). Macrophages are required for neonatal heart regeneration. *J Clin Invest* 124:1382–1392.
- Baggish AL, Wolfel EE, and Levine BD. (2014). *The Cardiovascular System at High Altitude*. Springer Publications, New York.
- Baibas N, Trichopoulou A, Voriadis E, and Trichopoulos D. (2005). Residence in mountainous compared with lowland

- areas in relation to total and coronary mortality. A study in rural Greece. *J Epidemiol Community Health* 59:274–278.
- Bartsch P, Saltin B, Dvorak J; Federation Internationale de Football Association. (2008). Consensus statement on playing football at different altitude. *Scand J Med Sci Sports* 18 (Suppl 1):96–99.
- Bayram F, Kocer D, Gundogan K, Kaya A, Demir O, Coskun R, Sabuncu T, Karaman A, Cesur M, Rizzo M, et al. (2014). Prevalence of dyslipidemia and associated risk factors in Turkish adults. *J Clin Lipidol* 8:206–216.
- Beall CM. (2000). Tibetan and Andean patterns of adaptation to high-altitude hypoxia. *Hum Biol* 72:201–228.
- Bender PR, Groves BM, McCullough RE, McCullough RG, Huang SY, Hamilton AJ, Wagner PD, Cymerman A, and Reeves JT. (1988). Oxygen transport to exercising leg in chronic hypoxia. *J Appl Physiol* (1985) 65:2592–2597.
- Benziger CP, Bernabe-Ortiz A, Gilman RH, Checkley W, Smeeth L, Malaga G, Miranda JJ; CRONICAS Cohort Study Group. (2015). Metabolic abnormalities are common among South American Hispanics subjects with normal weight or excess body weight: The CRONICAS cohort study. *PLoS One* 10:e0138968.
- Bernabe-Ortiz A, Carrillo-Larco RM, Gilman RH, Checkley W, Smeeth L, Miranda JJ; CRONICAS Cohort Study Group. (2017). Impact of urbanisation and altitude on the incidence of, and risk factors for, hypertension. *Heart* 103:827–833.
- Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS, Lurie K, Billingham ME, Harrison DC, and Stinson EB. (1982). Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. *N Engl J Med* 307:205–211.
- Brito J, Siques P, Leon-Velarde F, De La Cruz JJ, Lopez V, and Herruzo R. (2007). Chronic intermittent hypoxia at high altitude exposure for over 12 years: Assessment of hematological, cardiovascular, and renal effects. *High Alt Med Biol* 8:236–244.
- Bryant DM, O'Meara CC, Ho NN, Gannon J, Cai L, and Lee RT. (2015). A systematic analysis of neonatal mouse heart regeneration after apical resection. *J Mol Cell Cardiol* 79: 315–318.
- Buch J, Egeblad H, Hansen PB, Kjaergard H, Waldorff S, and Steiness E. (1980). Correlation between changes in systolic time intervals and left ventricular end-diastolic diameter after preload reduction. Non-invasive monitoring of pharmacological intervention. *Br Heart J* 44:668–671.
- Darehzereshki A, Rubin N, Gamba L, Kim J, Fraser J, Huang Y, Billings J, Mohammadzadeh R, Wood J, Warburton D, et al. (2015). Differential regenerative capacity of neonatal mouse hearts after cryoinjury. *Dev Biol* 399:91–99.
- de Mendoza S, Nucete H, Ineichen E, Salazar E, Zerpa A, and Glueck CJ. (1979). Lipids and lipoproteins in subjects at 1,000 and 3,500 meter altitudes. *Arch Environ Health* 34: 308–311.
- Dominguez Coello S, Cabrera De Leon A, Bosa Ojeda F, Perez Mendez LI, Diaz Gonzalez L, and Aguirre-Jaime AJ. (2000). High density lipoprotein cholesterol increases with living altitude. *Int J Epidemiol* 29:65–70.
- Dunn A, Lo V, and Donnelly S. (2007). The role of the kidney in blood volume regulation: The kidney as a regulator of the hematocrit. *Am J Med Sci* 334:65–71.
- Ezzati M, Horwitz ME, Thomas DS, Friedman AB, Roach R, Clark T, Murray CJ, and Honigman B. (2012). Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: National population-based analysis of US counties. *J Epidemiol Community Health* 66:e17.
- Faeh D, Gutzwiller F, Bopp M; Swiss National Cohort Study Group. (2009). Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. *Circulation* 120: 495–501.
- Faeh D, Moser A, Panczak R, Bopp M, Roosli M, Spoerri A; Swiss National Cohort Study Group. (2016). Independent at heart: Persistent association of altitude with ischaemic heart disease mortality after consideration of climate, topography and built environment. *J Epidemiol Community Health* 70: 798–806.
- Fiori G, Facchini F, Pettener D, Rimondi A, Battistini N, and Bedogni G. (2000). Relationships between blood pressure, anthropometric characteristics and blood lipids in high- and low-altitude populations from Central Asia. *Ann Hum Biol* 27:19–28.
- Fowles RE, and Hultgren HN. (1983). Left ventricular function at high altitude examined by systolic time intervals and M-mode echocardiography. *Am J Cardiol* 52:862–866.
- Ginouves A, Ilc K, Macias N, Pouyssegur J, and Berra E. (2008). PHDs overactivation during chronic hypoxia “de-sensitizes” HIF α and protects cells from necrosis. *Proc Natl Acad Sci U S A* 105:4745–4750.
- Grover RF, Lufschanowski R, and Alexander JK. (1976). Alterations in the coronary circulation of man following ascent to 3,100 m altitude. *J Appl Physiol* 41:832–838.
- Groves BM, Droma T, Sutton JR, McCullough RG, McCullough RE, Zhuang J, Rapmund G, Sun S, Janes C, and Moore LG. (1993). Minimal hypoxic pulmonary hypertension in normal Tibetans at 3,658 m. *J Appl Physiol* (1985) 74:312–318.
- Hansen J, and Sander M. (2003). Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia. *J Physiol* 546:921–929.
- Hart J. (2015). Heart disease death rates in low versus high land elevation counties in the U.S. Dose Response 13:pii: dose-response.14-021.Hart.
- Hirata K, Ban T, Jinnouchi Y, and Kubo S. (1991). Echocardiographic assessment of left ventricular function and wall motion at high altitude in normal subjects. *Am J Cardiol* 68: 1692–1697.
- Hoon RS, Balasubramanian V, Mathew OP, Tiwari SC, Sharma SC, and Chadha KS. (1977). Effect of high-altitude exposure for 10 days on stroke volume and cardiac output. *J Appl Physiol Respir Environ Exerc Physiol* 42:722–727.
- Hu H, Petousi N, Glusman G, Yu Y, Bohlender R, Tashi T, Downie JM, Roach JC, Cole AM, Lorenzo FR, et al. (2017). Evolutionary history of Tibetans inferred from whole-genome sequencing. *PLoS Genet* 13:e1006675.
- Hu Y, Sun Q, Li Z, Chen J, Shen C, Song Y, and Zhong Q. (2014). High basal level of autophagy in high-altitude residents attenuates myocardial ischemia-reperfusion injury. *J Thorac Cardiovasc Surg* 148:1674–1680.
- Hurtado A, Escudero E, Pando J, Sharma S, and Johnson RJ. (2012). Cardiovascular and renal effects of chronic exposure to high altitude. *Nephrol Dial Transplant* 27 (Suppl 4):iv11–iv16.
- Jain SC, Bardhan J, Swamy YV, Krishna B, and Nayar HS. (1980). Body fluid compartments in humans during acute high-altitude exposure. *Aviat Space Environ Med* 51:234–236.
- Jefferson JA, Escudero E, Hurtado ME, Kelly JP, Swenson ER, Wener MH, Burnier M, Maillard M, Schreiner GF, Schoene RB, et al. (2002). Hyperuricemia, hypertension, and proteinuria associated with high-altitude polycythemia. *Am J Kidney Dis* 39:1135–1142.
- Kacimi R, Richalet J-P, Corsini A, Abousahl I, and Crozatier B. (1992). Hypoxia-induced downregulation of beta-adrenergic receptors in rat heart. *J Appl Physiol* 73:1377–1382.

- Karliner JS, Sarnquist FF, Graber DJ, Peters RM, Jr., and West JB. (1985). The electrocardiogram at extreme altitude: Experience on Mt. Everest. *Am Heart J* 109:505–513.
- Keyes LE, Sallade TD, Duke C, Starling J, Sheets A, Pant S, Young DS, Twillman D, Regmi N, Phelan B, et al. (2017). Blood pressure and altitude: An observational cohort study of hypertensive and nonhypertensive Himalayan Trekkers in Nepal. *High Alt Med Biol* 18:267–277.
- Khalid ME, Ali ME, Ahmed EK, and Elkarib AO. (1994). Pattern of blood pressures among high and low altitude residents of southern Saudi Arabia. *J Hum Hypertens* 8:765–769.
- Klausen K. (1966). Man's acclimatization to altitude during the first week at 3,800 M. *Schweiz Z Sportmed* 14:246–253.
- Lau S, Patnaik N, Sayen MR, and Mestrlil R. (1997). Simultaneous overexpression of two stress proteins in rat cardiomyocytes and myogenic cells confers protection against ischemia-induced injury. *Circulation* 96:2287–2294.
- Levine BD. (2015). Going high with heart disease: The effect of high altitude exposure in older individuals and patients with coronary artery disease. *High Alt Med Biol* 16:89–96.
- Lundby C, Calbet J, van Hall G, Saltin B, and Sander M. (2018). Sustained sympathetic activity in altitude acclimatizing lowlanders and high-altitude natives. *Scand J Med Sci Sports* 28:854–861.
- Mahmoud AI, O'Meara CC, Gemberling M, Zhao L, Bryant DM, Zheng R, Gannon JB, Cai L, Choi WY, Egnaczyk GF, et al. (2015). Nerves regulate cardiomyocyte proliferation and heart regeneration. *Dev Cell* 34:387–399.
- Malconian M, Rock P, Hultgren H, Donner H, Cymerman A, Groves B, Reeves J, Alexander J, Sutton J, Nitta M, et al. (1990). The electrocardiogram at rest and exercise during a simulated ascent of Mt. Everest (Operation Everest II). *Am J Cardiol* 65:1475–1480.
- Martcorena E, Ruiz L, Severino J, Galvez J, and Penalzoa D. (1969). Systemic blood pressure in white men born at sea level: Changes after long residence at high altitudes. *Am J Cardiol* 23:364–368.
- Melillo G, Musso T, Sica A, Taylor LS, Cox GW, and Varesio L. (1995). A hypoxia-responsive element mediates a novel pathway of activation of the inducible nitric oxide synthase promoter. *J Exp Med* 182:1683–1693.
- Miele CH, Schwartz AR, Gilman RH, Pham L, Wise RA, Davila-Roman VG, Jun JC, Polotsky VY, Miranda JJ, Leon-Velarde F, et al. (2016). Increased cardiometabolic risk and worsening hypoxemia at high altitude. *High Alt Med Biol* 17:93–100.
- Mingji C, Onakpoya IJ, Perera R, Ward AM, and Heneghan CJ. (2015). Relationship between altitude and the prevalence of hypertension in Tibet: A systematic review. *Heart* 101:1054–1060.
- Mirrahimov MM, Rafibekova ZhS, Dzhumagulova AS, Meimanaliev TS, Murataliev TM, and Shatemirova KK. (1985). Prevalence and clinical peculiarities of essential hypertension in a population living at high altitude. *Cor Vasa* 27:23–28.
- Moore LG, Niermeyer S, and Zamudio S. (1998). Human adaptation to high altitude: Regional and life-cycle perspectives. *Am J Phys Anthropol Suppl* 27:25–64.
- Moret P, Covarrubias E, Coudert J, and Duchosal F. (1972). Cardiocirculatory adaptation to chronic hypoxia: Comparative study of coronary flow, myocardial oxygen consumption and efficiency between sea level and high altitude residents. *Acta Cardiol* 27:283–305.
- Mortimer EA, Jr., Monson RR, and MacMahon B. (1977). Reduction in mortality from coronary heart disease in men residing at high altitude. *N Engl J Med* 296:581–585.
- Myhre LG, Dill DB, Hall FG, and Brown DK. (1970). Blood volume changes during three-week residence at high altitude. *Clin Chem* 16:7–14.
- Nakada Y, Canseco DC, Thet S, Abdisalaam S, Asaithamby A, Santos CX, Shah AM, Zhang H, Faber JE, Kinter MT, et al. (2017). Hypoxia induces heart regeneration in adult mice. *Nature* 541:222–227.
- Nguyen AD, McDonald JG, Bruick RK, and DeBose-Boyd RA. (2007). Hypoxia stimulates degradation of 3-hydroxy-3-methylglutaryl-coenzyme A reductase through accumulation of lanosterol and hypoxia-inducible factor-mediated induction of insigs. *J Biol Chem* 282:27436–27446.
- Nikimaa M. (2002). Oxygen-dependent cellular functions—Why fishes and their aquatic environment are a prime choice of study. *Comp Biochem Physiol A Mol Integr Physiol* 133:1–16.
- O'Meara CC, Wamstad JA, Gladstone RA, Fomovsky GM, Butty VL, Shrikumar A, Gannon JB, Boyer LA, and Lee RT. (2015). Transcriptional reversion of cardiac myocyte fate during mammalian cardiac regeneration. *Circ Res* 116:804–815.
- Otsuka K, Norboo T, Otsuka Y, Higuchi H, Hayajiri M, Narushima C, Sato Y, Tsugoshi T, Murakami S, Wada T, et al. (2005). Chronoecological health watch of arterial stiffness and neuro-cardio-pulmonary function in elderly community at high altitude (3524 m), compared with Japanese town. *Biomed Pharmacother* 59 (Suppl 1):S58–S67.
- Pasini GF, Donato F, Buizza MA, Fantoni C, Gelatti U, Tani M, and Grassi V. (1999). Prevalence of risk factors for coronary heart disease in a mountain community in northern Italy. *G Ital Cardiol* 29:891–897.
- Polizzotti BD, Ganapathy B, Walsh S, Choudhury S, Ammanamanchi N, Bennett DG, dos Remedios CG, Haubner BJ, Penninger JM, and Kuhn B. (2015). Neuregulin stimulation of cardiomyocyte regeneration in mice and human myocardium reveals a therapeutic window. *Sci Transl Med* 7:281ra45.
- Porrello ER, Mahmoud AI, Simpson E, Hill JA, Richardson JA, Olson EN, and Sadek HA. (2011). Transient regenerative potential of the neonatal mouse heart. *Science* 331:1078–1080.
- Porrello ER, Mahmoud AI, Simpson E, Johnson BA, Grinsfelder D, Canseco D, Mammen PP, Rothermel BA, Olson EN, and Sadek HA. (2013). Regulation of neonatal and adult mammalian heart regeneration by the miR-15 family. *Proc Natl Acad Sci U S A* 110:187–192.
- Poss KD, Wilson LG, and Keating MT. (2002). Heart regeneration in zebrafish. *Science* 298:2188–2190.
- Reeves JT, Groves BM, Sutton JR, Wagner PD, Cymerman A, Malconian MK, Rock PB, Young PM, and Houston CS. (1987). Operation Everest II: Preservation of cardiac function at extreme altitude. *J Appl Physiol* (1985) 63:531–539.
- Richardson DW, Kontos HA, Raper AJ, Patterson JL, Jr. (1967). Modification by beta-adrenergic blockade of the circulatory responses to acute hypoxia in man. *J Clin Invest* 46:77–85.
- Savard GK, Areskog NH, and Saltin B. (1995). Cardiovascular response to exercise in humans following acclimatization to extreme altitude. *Acta Physiol Scand* 154:499–509.
- Semenza GL, and Wang GL. (1992). A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. *Mol Cell Biol* 12:5447–5454.
- Sharma S. (1990). Clinical, biochemical, electrocardiographic and noninvasive hemodynamic assessment of cardiovascular status in natives at high to extreme altitudes (3000 m–5500 m) of the Himalayan region. *Indian Heart J* 42:375–379.

- Sharma SC, Balasubramanian V, Mathew OP, and Hoon RS. (1977). Serial studies of heart rate, blood pressure and urinary catecholamine excretion on acute induction to high altitude (3658 m). *Indian J Chest Dis Allied Sci* 19:16–20.
- Sharma SC, Hoon RS, Balasubramanian V, and Chadha KS. (1978). Urinary catecholamine excretion in temporary residents of high altitude. *J Appl Physiol Respir Environ Exerc Physiol* 44:725–727.
- Shen Y, Chang C, Zhang J, Jiang Y, Ni B, and Wang Y. (2017). Prevalence and risk factors associated with hypertension and prehypertension in a working population at high altitude in China: A cross-sectional study. *Environ Health Prev Med* 22:19.
- Siebenmann C, and Lundby C. (2015). Regulation of cardiac output in hypoxia. *Scand J Med Sci Sports* 25 (Suppl 4):53–59.
- Simonson TS, Yang Y, Huff CD, Yun H, Qin G, Witherspoon DJ, Bai Z, Lorenzo FR, Xing J, Jorde LB, et al. (2010). Genetic evidence for high-altitude adaptation in Tibet. *Science* 329:72–75.
- Siques P, Brito J, Naveas N, Pulido R, De la Cruz JJ, Mamani M, and Leon-Velarde F. (2014). Plasma and liver lipid profiles in rats exposed to chronic hypobaric hypoxia: Changes in metabolic pathways. *High Alt Med Biol* 15:388–395.
- Suarez J, Alexander JK, and Houston CS. (1987). Enhanced left ventricular systolic performance at high altitude during Operation Everest II. *Am J Cardiol* 60:137–142.
- Temte JL. (1996). Elevation of serum cholesterol at high altitude and its relationship to hematocrit. *Wilderness Environ Med* 7:216–224.
- Tuder RM, Flook BE, and Voelkel NF. (1995). Increased gene expression for VEGF and the VEGF receptors KDR/Flk and Flt in lungs exposed to acute or to chronic hypoxia. Modulation of gene expression by nitric oxide. *J Clin Invest* 95:1798–1807.
- Villafuerte FC. (2015). New genetic and physiological factors for excessive erythrocytosis and Chronic Mountain Sickness. *J Appl Physiol* (1985) 119:1481–1486.
- Vogel JA, Hansen JE, and Harris CW. (1967). Cardiovascular responses in man during exhaustive work at sea level and high altitude. *J Appl Physiol* 23:531–539.
- Vogel JA, Hartley LH, and Cruz JC. (1974). Cardiac output during exercise in altitude natives at sea level and high altitude. *J Appl Physiol* 36:173–176.
- Voss JD, Allison DB, Webber BJ, Otto JL, and Clark LL. (2014). Lower obesity rate during residence at high altitude among a military population with frequent migration: A quasi experimental model for investigating spatial causation. *PLoS One* 9:e93493.
- Winkelmayer WC, Hurley MP, Liu J, and Brookhart MA. (2012). Altitude and the risk of cardiovascular events in incident US dialysis patients. *Nephrol Dial Transplant* 27:2411–2417.
- Wolfel EE, Groves BM, Brooks GA, Butterfield GE, Mazzeo RS, Moore LG, Sutton JR, Bender PR, Dahms TE, McCullough RE, et al. (1991). Oxygen transport during steady-state submaximal exercise in chronic hypoxia. *J Appl Physiol* (1985) 70:1129–1136.
- Wolfel EE, Selland MA, Cymerman A, Brooks GA, Butterfield GE, Mazzeo RS, Grover RF, and Reeves JT. (1998). O₂ extraction maintains O₂ uptake during submaximal exercise with beta-adrenergic blockade at 4,300 m. *J Appl Physiol* (1985) 85:1092–1102.
- Wolfel EE, Selland MA, Mazzeo RS, and Reeves JT. (1994). Systemic hypertension at 4,300 m is related to sympathoadrenal activity. *J Appl Physiol* (1985) 76:1643–1650.
- Woolcott OO, Castillo OA, Gutierrez C, Elashoff RM, Stefanovski D, and Bergman RN. (2014). Inverse association between diabetes and altitude: A cross-sectional study in the adult population of the United States. *Obesity (Silver Spring)* 22:2080–2090.
- Wozniak CJ, Baird BC, Stehlik J, Drakos SG, Bull DA, Patel AN, and Selzman CH. (2012). Improved survival in heart transplant patients living at high altitude. *J Thorac Cardiovasc Surg* 143:735–741.e1.
- Wyss CA, Koepfli P, Fretz G, Seebauer M, Schirlo C, and Kaufmann PA. (2003). Influence of altitude exposure on coronary flow reserve. *Circulation* 108:1202–1207.
- Xiao Q, Zhang G, Wang H, Chen L, Lu S, Pan D, Liu G, and Yang Z. (2017). A p53-based genetic tracing system to follow postnatal cardiomyocyte expansion in heart regeneration. *Development* 144:580–589.
- Xin M, Kim Y, Sutherland LB, Murakami M, Qi X, McAnally J, Porrello ER, Mahmoud AI, Tan W, Shelton JM, et al. (2013). Hippo pathway effector Yap promotes cardiac regeneration. *Proc Natl Acad Sci U S A* 110:13839–13844.
- Yue L, Fan Z, Sun L, Feng W, and Li J. (2017). Prevalence of essential hypertension and its complications among Chinese Population at high altitude. *High Alt Med Biol* 18:140–144.
- Zaobornyj T, Valdez LB, Iglesias DE, Gasco M, Gonzales GF, and Boveris A. (2009). Mitochondrial nitric oxide metabolism during rat heart adaptation to high altitude: Effect of sildenafil, L-NAME, and L-arginine treatments. *Am J Physiol Heart Circ Physiol* 296:H1741–H1747.
- Zimmerman LH, Levine RA, and Farber HW. (1991). Hypoxia induces a specific set of stress proteins in cultured endothelial cells. *J Clin Invest* 87:908–914.

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