©Journal of Sports Science and Medicine (2013) **12,** 205-206
http://www.jssm.org

Letter to editor

Does Man Age Faster at the Everest Peak? A Hypothesis Paper

Dear Editor-in-Chief

Survival of metazoan organisms is dependent upon their ability to generate energy through the process of mitochondrial oxidative phosphorylation. Phosphorylation carries the inherent risk of generating reactive oxygen species (ROS) (Kang et al., 2003) Low levels of ROS are utilized for signal transduction, but prolonged elevation of ROS results in oxidation of proteins, lipids and nucleic acids, leading to cell dysfunction or death. The oxygen gradient diffusion of capillaries is essential for cell survival. Oxygen delivery and utilization must be balanced, and maintenance of oxygen homeostasis in arterial blood is mediated by reflexes that are sensitive to oxygen decrease and by release of several factors like Hypoxic Inducible Factor (HIF), which plays a key role in this homeostatic regulation (Semenza, 2011). In response to hypoxia, cellular adaptive mechanisms induce expression of HIF, which in turn stimulates Vascular Endothelial Growth Factor (VEGF), important also in pregnancy (Wang et al., 2012), in tumor angiogenesis, during sleep apnea, typical of the elderly and in obese subjects.

Intermittent hypoxia represents a risk for sudden death, cardiac failure and certain forms of hypertension (Jain, 2007; Lavie, 2003), also for diseases involved with reduced oxygen diffusion due to an increase in the distance between the capillary bed and mitochondria. Chronic hypoxia, a common link of many diseases, induces adaptations in the tissue geometry, for example the human fetus develops oxygen tension values equal to the altitude of Mount Everest (PaO_2 = 28 mmHg) (Tonse and Raju, 2007). Considering that acute exposure above 5000 m without adaptation is not possible and less than 200 climbers have reached the Everest peak without supplementary oxygen, the PO_2 at high altitude is not comfortable for most climbers, and even though the Everest is the highest mountain in the world, probably it does not represent the limit of human tolerance. Life is possible at any existing altitude on our planet, Even Zubieta-Castillo quoted "life is possible anywhere on this planet, provided that adequate nutrition and housing are available, and enough time is allowed for slow adaptation" (Zubieta-Castillo et al., 2003).West reports that 5340 m is probably the altitude limit for permanent residents (West, 2009). Statistically, life expectancy at high altitude decreases with increasing altitude, considering that VO_2 max decreases by 9 % every 100 m above an altitude of 1100 m, and aging is characterized by decrease in VO_2 max of 1% per year (Wagner, 1996). There are many correlations between VO_2 max decreases in aging and in altitude. Both aging and altitude induce generation of ROS, which result in detrimental effects on structural and functional components of membranes (Lahiri et al., 2002). ROS are generated under hypoxic conditions and the accumulation of free radicals during life reduces the ability of tissues to remove them. Considering that life span is correlated with metabolism rate and mitochondria are the site of oxygen consumption (Sohal et al., 2007), the increases in HIF-1α in response to acute and chronic hypoxia have a crucial role in adaptation processes. Moreover high altitude results in lower birth rates in all races, considering the reduction in fertility (Verratti, et al., 2008), life on the Everest would theoretically be impossible because of the accelerating ROS production and aging.

If we consider that HIF regulates gene expression, recurrent sleep apnea that increases with aging and altitude, would all mimic chronic intermittent hypoxia (Edwards et al., 2010). We found a tight correlation among aging, hypoxia and ROS increase that might act through HIF-1α cell accumulation. Moreover aging, patients with heart failure or with chronic obstructive pulmonary diseases (COPD) are associated with muscle wasting, in turn correlated to chronic hypoxemia. Reducing hypoxemia in these patients improves force capacity (Salhi et al., 2010). Chronic hypoxia causes loss of force and power in human limb muscle similar to that occurring in aging (Ferretti, 1990). Many implications in oxidative pathophysiology are important for oxygen homeostasis, the rearrangement adaptation that occurs at tissue level during altitude and aging, modifies the diffusion distance between oxygen and mitochondria, so partly explaining the progressive decrease in maximum consumption of oxygen and the production of oxygen free radicals responsible for the oxidative damage in tissues during altitude and aging. Some authors highlight the decrease in intracellular ATP concentration as the metabolic sensor of the cell; while others hypothesize the existence of membrane pH dependent receptors. The gene expression of correlated factors in response to hypoxia would clarify the link among hypoxia, aging and the physiopathological bases of many diseases that share a common state of hypoxia. Intermittent hypoxia is more detrimental than chronic hypoxia, and intermittent hypoxia exposure is a cause of aging with ROS production. In parallel, intermittent exercise or excessive training with increases in ROS would damage the cellular clock for aging (Fehrenbach et al., 2001). When people that live at high altitude descend, they feel ill due to excess in oxygen, so both intermittent hypoxia and hyperoxia induce ROS production in the attempt to adapt, so PO_2 fluctuations disturb cell homeostasis. It is believed that the Everest is the limit for man, but other important factors have to be implied like solar radiation, exercise, and gender differences (Muza et al., 2001). Indeed, women living at high altitude are more susceptible to diseases and tend to die earlier, so altitude hypoxia through ROS generation seems to be an aging accelerator (Di Giulio et al., 2005). In altitude a greater amount of nitric oxide and ROS are produced that accel-

Received: 07 November 2012 / Accepted: 03 December 2012 / Published (online): 01 March 2013

erate aging. High altitude hypoxia increases death rate and decreases life-expectancy. In other words life expectancy on the Everest peak seems to be shorter, and the Everest model is useful to understand the correlation between oxygen supply and metabolism in order to find new strategies to prevent or delay the aging processes.

Camillo Di Giulio
Department of Neurosciences and Imaging, University of Chieti, Italy

References

Di Giulio, C., Cacchio, M., Bianchi, G., Rapino, C., and Di Ilio, C. (2005) Oxygen and life span: chronic hypoxia and hyperoxia as models for studying VEGF, NOS and HIF during ageing. *Respiratory Physiology & Neurobiology* **147**, 31-38.

Edwards-Bradley, A., O'Driscoll-Denise, M., Ali, A., Jordan-Amy, S., Trinder, J. and Malhotra, A. (2010) Aging and sleep: physiology and pathophysiology. *Seminars in Respiratory and Critical Care Medicine* **31**, 618-633.

Fehrenbach, E. and Northoff, H. (2001) Free radicals, exercise, apoptosis, and heat shock proteins. *Exercise Immunology Review* **7,** 66-89.

Ferretti, G. (1990) On maximal oxygen consumption in hypoxic humans. *Experientia* **46**, 1188-1194.

Jain, V. (2007) Clinical perspective of obstructive sleep apnea-induced cardiovascular complications. *Antioxidants & Redox Signaling* **9**, 701-710.

Kang, D. and Hamasaki, N. (2003) Mitochondrial oxidative stress and mitochondrial DNA. *Clinical Chemistry and Laboratory Medicine* **41**, 1281-1288.

Lahiri, S., Di Giulio, C. and Roy, A. (2002) Lessons from chronic intermittent and sustained hypoxia at high altitudes. *Respiratory Physiology & Neurobiology* **130**, 223-233.

Lavie, L. (2003) Obstructive sleep apnoea syndrome an oxidative stress disorder. *Sleep Medicine Reviews* **7**, 35-51.

Muza-Stephen, R., Rock-Paul, B., Fulco-Charles, S., Zamudio, S., Braun, B., Cymerman, A., Butterfield-Gail, E. and Moore-Lorna, G. (2001) Women at altitude: ventilatory acclimatization at 4,300 m. *Journal of Applied Physiology* **91**, 1791-1799.

Salhi, B., Troosters, T., Behaegel, M., Joos, G. and Derom, E. (2010) Effects of pulmonary rehabilitation in patients with restrictive lung disease. *Chest* **137**, 273-279.

Semenza, G.L. (2011) Hypoxia. Cross talk between oxygen sensing and the cell cycle machinery. *American Journal of Physiology Cell Physiology* **301**, 550-552.

Sohal-Rajindar, S. and Forster-Michael, J. (2007) Coenzyme Q, oxidative stress and aging. *Mitochondrion* **7**, 103-111.

Tonse, N.K. and Raju, M.D. (2007) Sir Joseph Barcroft: the 20th Century's Renaissance perinatal physiologist. *Neo Review* **8**, 311-312.

Verratti, V., Berardinelli, F., Di Giulio, C., Bosco, G., Cacchio, M., Pellicciotta, M., Nicolai, M., Martinotti, S. and Tenaglia, R. (2008) Evidence that chronic hypoxia causes reversible impairment on male fertility. *Asian Journal of Andrology* **10**, 602-606.

Wagner, PD. (1996) A theoretical analysis of factors determining VO_2max at sea level and altitude. *Respiratory Physiology & Neurobiology* **106**, 329-343.

Wang, K. and Zheng, J. (2012) Signaling regulation of fetoplacental angiogensis. *Journal of Endocrinology* **212**, 243-255.

West, J.B. (2009) Tolerance to hypoxia. *High Altitude Medicine & Biology* **10**, 203-206.

Zubieta-Castillo, G., Zubieta-Calleja, G.R., Zubieta-Calleja, L. and Zubieta-Calleja, N. (2003) Adaptation to life at the altitude of the summit of Everest. *Fizio Zh Journal* **49**, 110-117.

✉ **Prof. Camillo Di Giulio MD**
Department of Neurosciences and Imaging, University of Chieti-Pescara, Via dei Vestini, 31 Chieti Scalo 66010, Italy
E-mail: digiulio@unich.it