Abstracts From the 6th Chronic Hypoxia Symposium, October 8–15, 2016, La Paz, Bolivia

Dedicated to the Late Prof. Dr. Gustavo Zubieta-Castillo

Every two years the Chronic Hypoxia Symposium is carried out in order to gather scientists from around the globe to present their work and discuss aspects of chronic exposure to hypoxia. The first three symposia, The Effect of Chronic Hypoxia on Diseases at High Altitude, were held in La Paz, Bolivia at 3510 m, the “shrine of hypoxia” and location of the High Altitude Pulmonary and Pathology Institute (IPPA), the first high-altitude clinic in the world, created on July 9th, 1970 by the late Prof. Dr. Gustavo Zubieta-Castillo Sr. The fourth symposium was carried out jointly with the Global Hypoxia Summit at the Defense Institute of Physiology and Allied Sciences (DIPAS) in Delhi, India. The fifth and this one, the sixth, returned to La Paz. It was an itinerant meeting, starting the first day in La Paz at 3500 m, the second in the Tiahuanacu ruins (3800 m), the third day at Lake Titicaca (3800 m), the highest navigable lake in the world, and the fourth day in Chacaltaya at 5300 m, where the Glass Pyramid Laboratory, the highest laboratory in the world, is located. The spirit of this symposium is an open mind to different concepts about exposure and life under chronic hypoxia, with a criterion that adaptation to chronic hypoxia is successful and often misunderstood.

The Road to “Defeating Hypoxia” is a Timely Exposure to Chronic Hypoxia

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Acute exposure to hypobaric hypoxia can give rise to acute mountain sickness, and in some severe cases, high altitude pulmonary edema (HAPE) and high altitude cerebral edema (HACE), that can sometimes lead to the loss of life. However, once the acute phase evolves from gradual adaptation to a fixed “chronic hypoxia” altitude, following the Adaptation to High Altitude Formula (adaptation to high altitude = time/altitude), the organism does remarkably well. Life under chronic hypoxia, where an optimal hematocrit is reached for every fixed altitude, following a logarithmic curve in relation to time, is practically as normal as that at sea level. The cities of La Paz (3100–4100 m) and El Alto (4100 m) stand as living proof of this. Over 2 million inhabitants carry out perfectly normal lives, undisturbed by hypoxia and most even unaware of its existence. The lungs increase in volume, the right heart is mildly hypertrophied secondary to a normal adaptive pulmonary hypertension (relative to sea level). All the cells of the organism likewise adapt to a lower arterial oxygen arterial partial pressure (P_aO_2) but also to a lower arterial partial pressure of carbon dioxide (P_aCO_2), an essential component that linked to an increased hemoglobin explain the paradox of increased “tolerance to hypoxia” at high altitude. The higher the altitude, the more tolerance to hypoxia.

Life under chronic hypoxia is not only tolerable, but also is, in fact, favorable to improve or treat many pathological conditions such as asthma, coronary artery disease, obesity and even giving rise to improved longevity.

“Every living being, according to the genetic buildup—that determines their species, race and sex—has an optimal form of adaptation and the proof lies in a successful reproduction and survival at any altitude.” – Prof. Dr. Gustavo Zubieta-Calleja

Interindividual Differences in the Adaptive Response of the Lung to Hypoxia

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The adaptive response of the lung to hypoxia is dominated by the risk of potential development of lung edema on one side, and, on the other, by the need to develop an adaptive response allowing to preserve the oxygen diffusion-transport function. The edemagenic condition relates to the increased cardiac output and microvascular permeability. The rigidity of the extravascular interstitial matrix represents the main mechanism to resist edema formation: due to this peculiar feature, the increase in microvascular filtration leads to a corresponding remarkable increase in interstitial pressure that strongly buffers filtration. A further antiedemagenic mechanism is based on blood flow restriction to the septal microcirculation. This occurs by active vasoconstriction in the regions where edema tends to develop. A further cause of blood flow limitation in the septal capillary bed is due to the increase in the interstitial pressure that decreases the patency of the capillaries. The blood flow limitation in the septal capillary bed leads to increased perfusion of the corner vessels running at the edge of the alveoli; the overall increase in blood flow vascular resistance is matched by an increase in pulmonary artery pressure. A surprising finding is that in about 55% of subjects, DL_{CO} increased in hypoxia (exposure to 3500 m), reflecting an increase in conductance of the air blood barrier Dm that largely overruled the decrease in capillary blood volume (V_c). In about 25% subjects DL_{CO} remained unchanged in hypoxia while it decreased in 15%. We will explore how individual oxygen diffusion-transport features influence this response.

Interindividual Differences Concerning the Oxygen Diffusion-Transport Function in the Lung

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The oxygen diffusion/transport function is accomplished at the level of the air-blood barrier. Lung diffusion (DL_{CO}) is currently measured using carbon monoxide as a tracer gas that is not diffusion limited. Subcomponents of DL_{CO} can also be derived representing surface membrane diffusivity (Dm) and volume of blood present in the lung capillary, allowing oxygen-Hb binding (V_c). Subjects differed substantially in terms of DL_{CO} , Dm , and V_c . We attempted to estimate diffusion limitation in subjects exposed to 3850 m by determining the decrease of the $DO_2 / \beta \dot{Q}$ individual ratio, the so-called “equilibration index” (Piiper and Scheid, *Respir Physiol*, 1981), where DO_2 , the oxygen diffusion capacity, was calculated as $DL_{CO} \cdot 1.23$, $\dot{Q}$ was cardiac output, and β was the hemoglobin binding capacity for O_2 . A decrease in the “equilibration index,” potentially leading to diffusion limitation, was found in all subjects on exposure to hypoxia, yet, the lack of equilibration did not exceed 0.25 (0 corresponding to perfect equilibration, namely, no alveolo-capillary O_2 pressure difference). Subjects having a high equilibration index at sea level due to high DO_2 , high Dm , and a low heart rate have an advantage to prevent the fall of the equilibration index below 2, a critical value below which diffusion limitation occurs.

Potential Application of Cerium Dioxide Nanoparticles for Acute Pneumonia Treatment

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