Abstracts

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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 into gradual adaptation to a fixed “Chronic Hypoxia” altitude, following the Adaptation to High Altitude Formula:

$$\text{Adaptation to high altitude} = \frac{\text{time}}{\text{altitude}}$$

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 (3100-4100m) and El Alto (4100m) 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 (PaO2) but also to a lower arterial partial pressure of carbon dioxide (PaCO2), 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 perfectly 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”

Inter-individual 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 anti-edemagenic 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; 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, *DLCO* increased in hypoxia (exposure to 3500m), reflecting an increase in *Dm* that largely overruled the decrease in *Vc*. In about 25% subjects *DLCO* remained unchanged in hypoxia while it decreased in 15%. We will explore how individual oxygen diffusion-transport features influence this response.

Inter-individual 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. Diffusion occurs through the surface of the air-blood barrier (ABB) and of the red blood cells (RBC). Diffusion is therefore directly proportional to the overall extension of the alveolar surface and to the external surface of the RBC; conversely, lung diffusion is inversely proportional to the thickness of the ABB and of the RBC cellular membrane. The transport function occurs through the RBC flow through lung capillaries carrying oxygen bound to hemoglobin. The oxygen diffusion/transport function can be profitably discussed based on individual measurements of total lung diffusion properties and cardiac output (*CO*). Lung diffusion is defined by the overall diffusion (*DLCO*) and its subcomponents, namely: *Dm* (representing surface membrane diffusivity), and *Vc* (volume of blood present in the lung capillary allowing oxygen-Hb binding. Subjects differ substantially in terms of *DLCO, Dm* and *Vc*. Interestingly, subjects also substantially differ when considering an important ratio, namely *DLCO/CO*. This ratio defines indeed the kinetics of equilibration of oxygen partial pressure between alveoli and capillaries. We will explore how this kinetics differs among subjects due to individual changes in diffusion properties and cardiac output, in response to the need to increase the oxygen-diffusion-transport on hypoxia exposure that implies a decrease in partial pressure gradient for oxygen.

Potential application of cerium dioxide nanoparticles for acute pneumonia treatment

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Background

Cerium dioxide nanoparticles (CeO_2 NP) have antioxidant properties and also can alter membrane potential in mitochondria influencing cell respiration. In this study we check the idea that CeO_2 NP adsorbed on the silicon base has counter inflammatory, antioxidant and metabolic effects and can be possibly applied in pneumonia treatment.

Methods.

36 Rats Wistar males 5 month, 250-290 g were divided in five groups. 1) Intact animals, 2) i/p saline injection, 3) CeO_2 NP treatment, 4) experimental pneumonia (i/p LPS injection, 1 mg/kg), 5) experimental pneumonia treated by CeO_2 NP (2.5 mg/kg). Pulmonary ventilation and gas exchange were measured four times: before and 1, 3 and 24 h after LPS injection. The mRNA of TNF-α, Il-6, and CxCL3 were determined by RT-PCR. ROS-generation in blood plasma and lung tissue homogenate was measured by means of lucigenin- and luminol-enhanced chemiluminescence.

Results.

Endotoxaemia in the acute phase was associated with essential inhibition of metabolism: gradual decrease of V_E (by 72%) and V_{O2} (by 62%) 24 hour after LPS injection; pathological changes in lung morphology; enhanced expression of CxCL3 (by 68%); increase of ROS generation in blood (by 660%) and lungs (in 33%).

LPS-injected rats treated with CeO_2 NP did not demonstrated any V_E and V_{O2} reduction 1 hour after LPS-injection and increase of V_E (by 25%) and V_{O2} (by 20%) 3 hour after injection; this effect remained 24 hour after injection.

It should be knotted that CeO_2 NP treatment of control rats increased V_E by 20% and V_{O2} by 45% in comparison with first measurement after each introduction of the substance.

Treatment of LPS-injected rats with CeO_2 NP has led to diminishing in lung morphology pathological deviations; significant decrease of the expression of inflammatory markers: CxCL33 (in 7.1 times, $p < 0.01$), Il-6 (in 3.5 times, $p <0.05$) and TNF-α (in 2 times, $p=0.05$); significant reducing of ROS generation in blood (in 2.7 times, $p< 0.05$) and lung tissue homogenate (in 1.3 times $p< 0.05$).

Conclusion.

CeO2 NP significantly reduces morphological and functional pulmonary damage in course of experimental acute pneumonia. Discussing mechanism of this effect we propose two suggestions. First: CeO2 NP is powerful antioxidant, which protects lung tissue and, possibly, inhibits synthesis of cytokines. Second: treatment with CeO2 NP significantly accelerate metabolism and gives additional vigor to cells suffering with pneumonia.

Vihangam Yog helps in high altitude chronic hypoxia

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The basic biochemical reaction for energy production in the body depends on oxygen. Minimum level of oxygen is essential at tissue level to sustain that basic metabolic reaction at the required rate. If oxygen falls below the critical level, the body system switches to an anaerobic process which cannot sustain life for long. This deficiency at tissue level is known as hypoxia.

How can Vihangam yog help in high altitude hypoxia? There are two options: either we maintain the supply or we decrease the oxygen demand: 1. Oxygen transport to supply at the required consumption, 2. Acclimatizing by increasing the hemoglobin concentration of the blood, 3. The way in which yog can help is by reducing the demand by practicing yog at level of life force (Prana), we can regulate our basic metabolic rate, hence we are reducing the demand. There are ten pranas (life forces) in our body, each one having its designated function as and when needed. Hence our Basal Metabolic Rate (BMR) will be reduced, thus reducing the demand of oxygen needed to sustain life. It is not possible by other forms of yoga which only work at the level of the body.

The old age Vihangam yog was rediscovered by H.H. Shri Sadguru Sadafaldeo ji and this has presently been propagated by H.H. Shri Sadguru Swatantradeo ji across the globe. It teaches us and trains us to use this method of meditation based on the intimate relationship between ‘MIND’ and ‘PRANA’. By practicing it, our mind can be fully tamed and thereby, control over ‘Pranas’ (life forces) increases, which helps us in controlling and regulating our basal metabolic rate as discussed above, thus protecting us even from high altitude chronic hypoxia.

Media & Mountain Medicine A Commitment: Role and Impact of Media on Society and with Special reference to Newspapers role in Public Awareness

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Media is Dynamic and plays a important and significant role in our society today. Media is all round us 24/7 and 365 days, in newspapers - Daily, Weekly or Monthly, Magazines, books and journals & periodicals, The Television channels show News and programs on varied subjects be it education, agriculture, sports, science and technology, health and fitness or entertainment.
The Radios broadcast music, news and public awareness programs on FM/ MW/SW Radio stations.
The new age media includes the Internet and other social media Twitter, Insta gram, Facebook and others.
Media is a WINDOW to the world, without which people and the society would be ignorant & isolated from what is happening around them and in the world, including the highest human habitats like those in the cities of La Paz (3100m to 4100m) and El Alto (4100m). Media is present even on the summit of Mt. Everest (8842m), the highest point in the world.

Life in high altitude conditions

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I have always accepted and endorsed both Prof. Dr. Gustavo Zubieta-Castillo (Sr) and Prof. Dr. Gustavo Zubieta-Calleja (Jr) whenever they mentioned that life is possible on top of Mt Everest. I never doubted. I have a lot of supporting evidence which I wish to share with the rest of the world, during this wonderful meeting at very high altitude in Chacaltaya (5230m) where I deliver my talk for the second time.

Life does exists at extreme conditions of heat, pressure, temperature, radiation etc. We have functional life at the deepest part of the sea and at very high altitude. Life started at the bottom of the sea and birds fly for long hours at very high altitudes during their migration. People migrated to live and reproduce at high altitudes. The secret of life adaptation is not well understood. Scientists have designed their studies to find out the problems faced during their adaptation. Limited efforts are made to realize how life has sustained for long periods of time at extreme conditions. The most common house hold pest, cockroaches have survived severe radiations, heat and cold and even toxic pesticides, to which they adapt and cannot eliminate them.

Plants which normally grow at a particular rate under normal conditions, are found yielding at a higher rate when their life is threatened, as noted in young mango plants when pruned, they flower and yield fruit earlier. We are aware of the longevity in plants when they are Bonsaied. Similar life prolongation is noted in humans and animals under hypoxic conditions.

Longevity of life under hypoxic conditions is well established apart from a healthier life being assured. Lowlanders under hypoxic condition and highlanders under hyperbaric conditions will have initial problems, which get adjusted. On long stays, with generations living in those environments, there will be a genetic adaptation, which is applicable to all forms of life.

Physical and mental performance improves at higher altitudes. Hypoxia makes other dormant parts of the human brain, function and hence great philosophers and religious giants frequently visited high altitudes.

When these environments are altered by any man-made developments, it hampers the process of natural adaptation. Many toxins are now found causing environmental damage at various levels. This is evidenced by the unreasonable usage of medication. Living in harmony with nature, seems to be the ultimate solution. The effect seems to be more evident on life at high altitudes. Let us preserve high altitude conditions for better health, for quality longevity.

Let the dream of the Parvatha Guru (Mountain Guru), Gustavo Zubieta-Castillo Sr., come true.

Mountains – Law - Ethics

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“Don’t look up at the mountain, climb it” – Thus Said Swami Vivekananda. Climb the mountain we can see the world, not so world can see us. When a goal matters enough to a person, that person will find a way to accomplish what first seemed impossible.

Mountains therefore instigate us to make an adventurous attempt which has enormous environmental, socio economic and cultural value comprising vitally important resources and functions that benefit society both directly and indirectly: as regulators of climate and water resources ; containing important water reserves and providing us with fuel as sanctuaries of a large diversities ecosystems, with unique and exclusive species and an extraordinary variety of landscapes, communities languages and cultures, as studying grounds for disciplines such as geology and biology and as ideal settings to develop environmental education activities.

There has been a need to enact loss / declarations on mountain protection having a large international tradition linked growing awareness of mountaineering community towards environment, as well as negative effects caused by the increase and massification of mountains sports of tourism activities on mountain ecosystem and local communities

The article presents certain principles in believing that freedom to practice mountaineering depends on the enormous value of mountain areas which are often the sources of products essential to human kind as a whole.

The role of mountain tourism is not only in supporting local communities but the misuse of existing resources may lead to the loss of biodiversity, massive or intrusive changes to the landscape, climate change and pollution due to overuse of sensitive areas.

Several declarations made by various mountaineering organizations have insisted on accepting the risks and assure responsibility leading to the balance of goals with skills and equipment, adopting fair means and reporting honestly. The declarations also insist to strive for best practice and never stop learning by being tolerant, considerate and help each other for protecting the wild and natural character of mountains and cliffs in order to support local communities and their sustainable development.

The values or otherwise termed as ethics of mountaineering connotes human dignity, life, liberty and happiness; intactness of nature, solidarity, self actualization, truth and adventure.

The attraction of sports climbing depends upon utilising opportunities provided to improve climbing standards and techniques resulting in to experience the pure fun of climbing with the fear of falling greatly reduced and enhancing aspirations of climbers to take the first step on to rock outside in relative safety, gradually learning about widening their climbing experience and having broad based exposure to an adventurous elevated and higher vision improving the social behaviour and to fight against the killers of the virgin nature it also improves to have better coexistence with the neighbourhood in spite of diversities and multidirectional cultural variations

The catastrophe resulted due to earthquake that shook Nepal living thousands of people standards in remote locations beyond the access of roads and helicopters; in a land of expedition the world food programme brought food and relief items those in greatest needs opened an access to humanitarian relief

Respect the mountains are the key slogan to promote sustainable mountain tourism through a global network of volunteers who activated significant step in mountain protection in their respective territories.

The risk, responsibility duty of care and liability insisted actions to reduce the risk of litigations against ourselves in taking actions to reduce the possibility of contributing any harms to others

Mountaineering enabled by legal and ethical foundation dictated that "If we were afraid of failures, we don't deserve success- we make a living by what we get, but we make a life but what we give".

Rearrangement of neuroendocrine systems in the mountains

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The aim of the research was to study the functional state of the anterior pituitary, thyroid, adrenal and reproductive glands and their relationship with the chronic exposure to high altitude factors.

The determination of the level of adrenocorticotropic hormone and thyroid-stimulating the pituitary gland, adrenal hormones - cortisol, thyroid gland - thyroxine and triiodothyronine, sex glands - testosterone and biogenic amines of adrenal medulla by spektroflyuorometric and immunosorbent methods for determining levels of hormones.

Functional state of the endocrine systems of mountaineers, high altitude natives (at an altitude of 2800 m and 3600 m above sea level) is characterized by reduced levels of the organism, and economical operation, which allows for normal life, they work and do heavy physical work in specific conditions of mountains. Reduced activity of the pituitary-adrenal system, evidence of a transition body functioning at a more economical level of regulation by minimizing the reaction of peripheral structures. Elevated levels of norepinephrine, dopamine, serotonin contribute to the optimal functioning under prolonged exposure to high altitude factors. Increased levels of TSH, T_4 and norepinephrine at a relatively low level of T_3 is a response to the cold. Reduced secretion of sex hormones (testosterone in men and women) demonstrates the mobilization of strategic reserves of the endocrine system and the narrowing of the functional reserves of the organism.

Why is it not possible to predict, through tests at sea level, who will have AMS?

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Some people don't present AMS on several altitude exposures, however, unexplainably, they may have it on some occasions. Several tests have been tried in order to determine who will have AMS, however, none up-to-date are able to achieve with absolute certainty who will get AMS. Some tests have been developed by having subjects breathe a hypoxic mixture. Others have created a protocol of testing while doing exercise, and some other techniques.

However none have been successful. We have seen, diagnosed and treated successfully, over many years of work at high altitude, patients with AMS of different intensity, some having undiscovered pathologies. For example inter-auricular communications, nephropaties, leading to essential hypertension, cardiac arrhythmias, presence of a kidney stone that does not block the urine pathway completely, abnormal arteries in the kidney, secuelae of pulmonary disease, with localized fibrosis, relative anemia due to poor bone marrow response, falciform anemia, and many others.

However those that apparently have no evident disease, can present severe cases of dehydration, particularly while doing exercise at high altitude. This of course, can be quite debilitating and if pushed beyond rationale can lead to severe complications. Performing a very precise diagnosis is difficult and there is still much to study in order to understand hypoxia throughly.

One of the explanations for the occasional presence of AMS could be there presence of sub-clinical viral infections. In the Children at High Altitude International Consensus, we are quoted as having written in our book that some cases of HAPE have a viral origin. We live with viruses, and when the virus is not so aggressive and not present in sufficient quantities, the organism has an internal struggle that uses up the energy. If the person ascends to the mountain in this conditions, his reserve to face hypoxic stress is limited and hence complications appear. Likewise if the person prior to the ascent had a different food, with unusual spices, or with unusual bacterias, then there is an inflammation of the bowels and the endothelial cells of the gastro-intestinal tract particularly at the colon level, may not be able to absorb water as efficiently as under normal circumstances. This can lead to a more severe case of dehydration and hence AMS. There are probably many other factors which include stress from other psychological difficulties, or even exposure to toxics that are inhaled and produce inflammation in the respiratory tract. Furthermore, those doing training at high altitude can overdue the exercise efforts, with great willpower, leading to very increased pulmonary artery pressure and hence a dilated right heart. This overcharged effort of the muscle cells in the right heart can give rise inflammation and micro-lesions that render the heart mildly insufficient in its capacity for pumping blood. On going higher in a sports competition, the optimal heart function is diminished and hence AMS can appear. This is due to the fact that the Adaptation to High Altitude Formula has not been respected in relation to time, where an adequate and timely increase of red blood cells is trascendental thereby generating Subacute High Altitude Heart Disease.

CO2 reactivity, a tool for prevention of HACE (High Altitude Cerebral Edema): Hands-on workshop

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La reactivad vascular cerebral al CO_2 es un mecanismo fisiológico adaptativo que regula el flujo sanguíneo cerebral de acuerdo a las necesidades metabólicas. Este mecanismo se ha empleado para medir el grado de severidad de las lesiones cerebrales traumáticas, metabólicas y en diferentes encefalopatias. Este mecanismo es el último componente de la autorregulación vascular cerebral que se pierde indicando un grave pronóstico. Sin embargo, en condiciones de normalidad este mecanismo puede evaluarse al inducir hiperventilación o hipoventilación y traduce disminución del flujo sanguíneo cerebral o aumento, respectivamente y consecuentemente pueden observarse cambios clínicos y metabólicos,eléctricos. Por un mm Hg de CO_2 disminuido se reducen 4 ml de flujo sanguíneo, aunque sabemos que el flujo varia en diferentes sitios anatómicos cerebrales. Esta medición se realiza invasivamente y con equipos sofisticados. En forma no invasiva es posible estudiar estos cambios a través de sistemas de capnografia, BIS (Indice Biespectral), Doppler transcraneal y Espectroscopia cercana al infrarrojo (NIRS).

En condiciones geográficas definidas por la altitud sobre el nivel del mar el nivel sanguíneo CO_2 cambia estrechamente conforme se incrementa la altitud del CO_2 y del mismo los procesos adaptativos cerebrales se modifican para permitir un adecuado equilibrio entre el metabolismo y el flujo.

Por otro lado, existen tablas definidas del comportamiento gasométrico y metabólico para ajustar el grado de "hipoxia" con el nivel de CO_2 y de su altitud sobre el nivel del mar. Sin embargo, estas tablas propuestas nunca se han correlacionado con los cambios en los sistemas de monitoreo cerebral y respiratorio antes propuestos.

Conocer el comportamiento de los gases arteriales a diferentes altitudes sobre el nivel el mar y relacionarlos con el grado de reactividadad al CO_2 tienen importantes implicaciones para muchas patologías cerebrales y también para condiciones de normalidad.

Es por ello que se propone desarrollar un taller de monitoreo cerebral y respiratoria en este congreso a diferentes altitudes sobre el nivel del mar en individuos nativos con más de 40 dias de vida en el medio habitual vs viajeros sin el proceso de adaptación habitual.

Low Altitude Peripheral Edema (LAPE): The opposite of HAPE or HACE.

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Millions of high altitude permanent residents, born at high altitude, living normal lives, doing sports, sleeping well, reproducing, enjoying entertainment occasionally descend to sea level, for work or leisure. This is a change where the organism perfectly adapted to chronic hypoxia is suddenly exposed to a hyperoxic environment and needs to adapt to the new circumstance. Although no alarming symptoms and signs such as those that can be seen in Acute Mountain Sickness exist like headaches, nausea, vomiting, there are signs that show evident changes in the body. One of the most striking is: edema of lower limbs, that becomes more pronounced at 2 weeks of stay. Although there may be an initial edema due to long airplane travel times, this one usually goes away within one or two days. However, after around 2 weeks, a positive Godet sign develops in both legs that can be quite impressive. The Godet sign, found by pressing during a few seconds on the skin in front of the Tibia, displaces excessive fluid found in the interstitial subcutaneous spaces and gives rise to the formation of an evident concave impression. This sign is found in patients with cardiac insufficiency, renal insufficiency, anasarca with low blood protein levels or inflammation.

If a physician would evaluate one of the high altitude residents, at that moment, he would surely think of cardiac insufficiency, and may event start treatment with diuretics or digitalis.

Possible mechanisms involve an increase of Sialic acid, found above or borderline of the normal maximun limits in 4 subjects. Urine tests also showed an acid pH = 6.0, in spite of been on vegetarian diets, on a recent trip to India.

Going to high altitude there is central edema and that is why Acute Mountain Sickness, High Altitude Pulmonary Edema and High Altitude Cerebral Edema, occur. Conversely on going to sea level, peripheral edema occurs. Going higher, oxygen needs to be transported preferably to the life sustaining organs: brain, heart and lungs, whereas going lower there is “excessive” amounts of oxygen and peripheral edema occurs as a defense mechanism to reduce oxygen transport to the life sustaining organs, as it is sensed toxic. The hematologic adaptation with a decrease of the hematocrit to sea level values, is linear and takes around 20 days, going from 3500m. Hence, once the hematocrit is at the optimal values for sea level, the peripheral edema decreases and is not as evident. Consequently the Altitude Adaptation Formula stands valid.

Rebuilding of carbohydrate and lipid metabolism under hypoxia: Regularities and therapeutic possibilities

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Previously, we have found that the effects of chronic (staying in midlands) or moderate periodic hypoxia as well as hypoxic preconditioning is accompanied by beneficial rebuilding in lipid and carbohydrate metabolism in human and animals: a reduction of total cholesterol and its fractions in blood plasma, a hypoglycemic reaction or normalization of elevated blood glucose, and a decrease of impaired glucose tolerance [Portnichenko V., Portnychenko A. et al., 2008-2016]. This metabolic rebuilding has a phase character during the adaptation to hypoxia and following deadaptation. We have identified the hypometabolic, shift, hypermetabolic and adaptive phases. Changes in metabolism during hypoxia occur in a consecutive manner and mediate by induction and repression of target genes following activation of hypoxia responsible signal ways and transcription factors. In particular, we showed the alternate transactivation of HIF-1alpha and -3alpha subunits, and the restructuring of glucose transport by consecutive induction of GLUT-4 and -1 in rat myocardium and lungs. Mitochondrial respiration is consequentially shifted from down - to up- regulation, and from carbohydrate to mainly lipid substrate using. In human, we found attenuation of transcriptional regulator of cholesterol synthesis SREBP-1, leptin and insulin-like growth factor IGF-1 levels in blood plasma under prolonged hypoxic conditions, as well as positive correlation with HIF-dependent protein IGF-1 and HDL-cholesterol level. In middle-aged people with metabolic disorders (metabolic syndrome, diabetes mellitus, dyslipidemia), favorable influence of staying in midlands, moderate acute or periodic hypoxia was found, but metabolic pathology was associated with altered pattern of regulatory protein expression. The data suggest the close relationship between carbohydrate and lipid metabolism under hypoxia, and evidence the possibility of hypoxic correction of metabolic disorders as diabetes, dyslipidemia and metabolic syndrome based on phase processes of metabolic rebuilding.

Modification of the Adaptation to High Altitude Formula

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Adaptation to high altitude is trascendental for life to go on. It is a time and altitude dependent phenomena, because the organism needs the adequate time to build the defense mechanisms to face environmental changes. Quoting the late Gustavo Zubieta-Castillo "The organic systems of human beings and all other species tend to adapt to any environmental change and circumstance within an optimal period of time, and never tend towards regression which would inevitably lead to death".

$$\text{Adaptation to high altitude} = \frac{\text{time}}{\text{altitude } \Delta}$$

It is important to note that altitude changes require adaptation going both ways: going up in altitude or for high altitude residents going down. This formula was originally developed using the changes in altitude going higher, because it was thought worldwide that the normal physiology of the body was developed at sea level, only. However, high altitude residents are perfectly adapted to life in their own environment. Hence it has been found convenient to include in the formula, in the denominator "altitude Δ" i.e. altitude change, instead of only the term "altitude". This, we find trascendental because the organism of high altitude residents going down to sea level, have to adapt to the "relative hyperoxic environment". It is wrongly assumed that for high altitude residents, going to a lower altitude where there is more oxygen pressure, as a result of a higher barometric pressure, is beneficial. We strongly question this, as high altitude residents, being born, developed and carrying out normal lives in the mountain cities of the world living in perfect harmony with our environment. We, as Andean high altitude residents, have higher hematocrit and hemoglobin values, as the fundamental compensating biological response. All living beings, humans, animals and plants and presumably other microscopic organisms suffer biologic changes on barometric pressure changes. In other words, physical changes in the environment, induce biological changes. The rules governing physics are imbedded within biology.

This trascendental formula of Adaptation is not only useful for high altitude adaptation, but rather can be used for any type of adaptation, where the organism in order to survive, needs to find the most energy efficient, fastest rebuild or healing of the system. For example with a wound in the skin. When the two borders are sutured, the healing process takes around 1 week. This would be:

Healing Adaptation = time/tissue.

This formula changes in time if the tissue is skin or bone, the later requiring a longer time of a few months. This formula varies with age, taking longer for the older people.

Adaptation to healing = time/Age.

It should be well understood, that the healthier the subject, the better the adaptation. But it also applies to allergic reactions to mosquito bites in those not habituated to them in comparison to those living in those areas. Likewise a viral aggression like flu, has a latent period of immunity that follows the same rule:

Adaptation to viral aggression = time/type of viral agent.

This formula has other additional variables like nutrition, stress and aggressiveness of the viral agent. Furthermore it also applies to adaptation to smell. When a new perfume is smelled for the first time it is very strong, but persistent use of it changes the capacity of sensing it.

Adaptation to smell = time/scent.

Muscle adaptation to exercise also follows the same formula:

Adaptation to exercise = time/exercise Δ.

The more exercise, the greater the hypertrophy of the muscles and vice-versa.

Adaptation to life = time/Age.

In conclusion the Adaptation formula is a trascendental formula that applies to all biological adaptation process in the survival mechanism of all living beings.

Neural Mechanisms Involved in Autonomic and Respiratory Changes in Rats Submitted to Short-Term Sustained Hypoxia

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Humans ascending to high altitudes are submitted to sustained hypoxia (SH), activating peripheral chemoreflex with several autonomic and respiratory responses. We analyzed the effect of short-term SH (24 hours, $FIO_2$10%) on the cardiovascular parameters in non-anesthetized rats and on the processing of cardiovascular and respiratory reflexes using *in situ* and *in vitro* preparations. SH produced hypertension in awake rats and increased the basal sympathetic activity in an *in situ* preparation and these effects may be related to changes in respiratory-sympathetic coupling.

SH increased both the sympatho-inhibitory and bradycardiac components of baroreflex and the sympathetic and respiratory responses of peripheral chemoreflex. Electrophysiological properties and synaptic transmission in the *nucleus tractus solitarius* (NTS) neurons, the first synaptic station of afferents of baro- and chemoreflex, were also evaluated using brainstem slices (*in vitro* studies). The 2nd-order NTS neurons were identified by previous application of fluorescent tracer onto carotid body for chemoreceptor afferents or onto aortic depressor nerve for baroreceptor afferents. SH increased the intrinsic excitability of NTS neurons. Delayed excitation, caused by A-type potassium current (IK_A) was observed in most of NTS neurons from control rats. The IK_A amplitude was higher in identified 2nd-order NTS neurons from control than in SH rats. SH also blunted the astrocytic inhibition of IK_A in NTS neurons and increased the synaptic transmission in response to afferent fibers stimulation. The reduction of glial cell density was also observed after SH protocol. Therefore, short-term SH produces changes in structural and functional integrity of glial cells, which are essential for neuronal activity and may contribute to the increase in cardiovascular reflex sensitivity (baro- and chemoreflex) and the development of hypertension in awake rats.

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PROSPECTIVE VALIDATION OF FRAMINGHAM CRITERIA FOR CONGESTIVE HEART FAILURE DIAGNOSIS IN A HIGH-ALTITUDE POPULATION

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Purpose: To determine the validity of Framingham criteria for heart failure diagnosis in a high-altitude population.

Material and Methods: This is a prospective, observational, descriptive and transversal study. The study population was comprised of 97 inpatients hospitalized at Internal Medicine Service at Hospital Nacional del Centro - EsSalud Huancayo, located at an altitude of 3240 meters above sea level. Patients included presented with dyspnea on exertion or at least one major Framingham criterium. Echocardiograms were performed with a Sonos 1000 echocardiographer, with color Doppler, B-mode and M-mode techniques. Dichotomous variables were analyzed by Mantel – Haenszel chi square test. A p value <0.05 was considered significant.

Results: Most patients were male (51.6%). Mean age was 69.55 years. A total of 73.2% of patients were elderly (n=71). The most frequent major criteria found were: cardiomegaly (88.9%), hepatojugular reflux (79.2%) and jugular engorgement (69.4%). The most important minor criteria were: exertional dyspnea (91.7%), pleural effusion (69.4%) and lower limb edema (58.3%). Framingham diagnostic criteria were present in 98.6% of patients with heart failure but had a specificity of only 12%. The specificity rose to 76% by using 4 major criteria and to 100% when using 5 criteria. Unfortunately, the sensitivity the sensitivity falled in the firstcase to 62.5% and to 31.9% in the latter.

Conclusions: Framingham criteria are highly sensitive but nonspecific for the diagnosis of heart failure in high-altitude populations.

DEVELOPMENT AND VALIDATION OF NEW SEPSIS CRITERIA AT HIGH-ALTITUDE

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ABSTRACT

INTRODUCTION: Current sepsis diagnostic criteria lose precision at high altitude due to physiological variation in vital functions. Because of that, it is necessary to elaborate new sepsis diagnostic criteria, especially designed for its use at populations living at 2000 meters above sea level or higher altitudes.

METHODS: This is a prospective, longitudinal and observational study, that took place at EsSalud Regional Hospital at Huancayo. Two cohorts were studied: a derivation cohort (394 patients) and a validation cohort (123 patients). A total of 147 adult patients with sepsis diagnosis and 247 healthy controls were included in the derivation cohort. Sepsis was confirmed with cultures, and diagnosis of infection was made according to CDC and McGeer criteria, in patients admitted to Intensive and Intermediate Care Unit from January 2007 to April 2008. Each case was followed up to discharge or death. With the obtained data, new diagnostic models were devised. A validation cohort of 72 patients with sepsis, 51 hospitalized patients without sepsis and 120 non hospitalized normal subjects was developed (validation cohort) with patients admitted to Internal Medicina Seervice from January 2012 to December 2013. Diagnostic criteria were evaluated with 2x2 tables, and specificity, sensitivity, negative and positive predictive values, as well as ROC AUC values were determined. Relative risk values and 95% confidence intervals are presented.

RESULTS: A total of 10 physiological variables were obtained to develop the new criteria. Three of them were selected: respiratory rate >23, temperature > 37.8 ºC or 37.5 ºC and heart rate > 85 beats/minute. More specific alternative diagnostic criteria selected were: Criterium 10 (ALT10) characterized by a RR >23, HR > 85, T > 37.5ºC and Leukocytes >10000 or <4000 or bands >5% or neutrophils > o = 70%; Criterium 22 (ALT 22): RR >23, HR > 85, T > 37.8ºC, Leukocytes >10000 o <4000 or bands >5% or neutrophils> o = 70%. ALT10 and ALT 22 sensitivity were superior to that of classical criteria: 100% and 99.3% versus 95.1%, respectively. Validation in hospitalized patients without sepsis revealed similar results, with ALT10 and ALT22 reaching 100% sensitivity. Specificity remained around 83.7- 84.8% when using the two alternative criteria in the derivation cohorts, while ti was 72% when using classical criteria.

CONCLUSIONS: Current sepsis criteria have limited specificity for diagnosis at high – altitude populations. The use of the new diagnostic criteria may decrease the rate of non – diagnosed patients from 5% to 0%, while increasing specificity from 72% to 84.8%.