Abstracts

8th CHRONIC HYPOXIA SYMPOSIUM

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MONDAY

Chronic Hypoxia: a remarkable stimulus for enhanced survival

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In 1921, Joseph Barcroft came from Cambridge University to perform research in a laboratory mounted in a train wagon in Cerro de Pasco (4,300m), Peru. After two months of research, he returned to England and wrote, “All dwellers at high altitude are persons of impaired physical and mental powers”. It is assumed that highlanders due to those characteristics are “inferior”. This generated a totally wrong misconception that continues until our days, and it has to stop. Over 2 million people living between 3,100m and 4,100m in the neighboring cities of La Paz and El Alto in Bolivia, are a standing proof that high altitude residents carry out perfectly normal lives. We are born, develop, practice sports, have children, participate in sports, and have pleasant lifes. We have previously shown that there is extended longevity at high altitude. Our sportsmen are winning more and more competitions by very significant time differences with the second and the rest of the competitors. Our brains, hearts and retinas have greater vascularity and hence not only perform optimally but also are less prone to stroke and myocardial infarction. We hardly ever have asthma crises at high altitude. The incidence of lung cancer at high altitude is much lower than at sea level.

One of the most significant threats to humans in these times has been the COVID-19 Pandemic. We have successfully shown that the incidence and case fatality rate is lower at high altitudes as compared to sea level. We feel safer at high altitude and have shown a greater chance of survival during the pandemic. We have previously affirmed that sea level residents (as compared to high altitude dwellers) have poor tolerance to hypoxia. Nevertheless, with adequate adaptation, it is possible to climb to the summit of Mt. Everest without oxygen.

High altitude life under chronic hypoxia is a healthy stimulus for the metabolism of living beings. It is like performing exercise that stimulates favorably not only the muscles but also the heart, the lungs, the kidneys, and all the organs of the body along with favorable metabolic and genetic expressions to survive under low oxygen pressures. This has important implications even for space travel as in a space capsule the ambient should be of the pressure of the high altitude cities of La Paz (3,100-4,100m) and El Alto (4,100m) and life outside of our planet.

In conclusion, we now affirm that the high altitude resident that has optimal physical and mental powers and is provided with a physiological advantage that grants him an enhanced chance for survival and extended longevity.

MONDAY

Factors affecting the exercise performance of highland natives in the Andes and Himalayas.

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Highland-native populations in both the Andes and Himalayas have enhanced exercise capacity in hypoxia. Previous work on Andean populations has clarified the importance of developmental effects to explain this exercise advantage. However, direct evidence supporting developmental effects in Tibetan-derived populations is lacking. In contrast, for both highland-native groups, the importance of genetic factors is becoming increasingly clear. In the case of Tibetans, genomic work implicates two Hypoxia Inducible Factor-alpha (HIF-alpha) genes (EPAS1 and EGLN1) that have been shaped by past natural-selection and affect Hb-concentration. Our research group has conducted similar studies on Peruvian Quechua and we have also identified several SNPs within the EGLN1 gene that were top hits in a selection scan. From genome-wide association (GWAS) analysis performed on a total sample of n=429 Peruvian Quechua, we identified five SNPs in or near EGLN1 that were associated with higher VO2max in hypoxia (rs1769793, rs2064766, rs2437150, rs2491403, rs479200). In this talk, we review some of the developmental and genetic work, and introduce our more recent studies of exercise capacity in Sherpa populations in Nepal at an altitude of 4,240 meters.

MONDAY

Beneficial effects of "PRANAYAMA" (regulated breathing) at high altitude hypoxic conditions – a new thought

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Mountaineer and scientist,
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The ancient four types of breathing technique initiated by Patanjali (2nd-century BCE-4th century CE) is an exercise for physical detoxification and mental wellness, a component of yogic practice from India. There is a strong belief that pranayama (Prana means life energy and Yama means control) was discovered 7000 years ago and has gained popularity of late in the western world as it has proved beyond doubt with scientific evidence of health benefits. Breathing is regulated by physiological, psychological, and environmental factors. Amongst the top five pranayama exercises, breath retention (Kumbaka pranayama) has proved to combat early symptoms of AMS. Pranayama has been proved by high altitude dwellers like native high landers, Sadhus, and Yogi meditating in Himalayan High altitude conditions (above 4500 meters). Modern science and researchers (the author was part of the expedition team) have shown evidence that subjects practicing pranayama control all five breathing cycles, which are constantly influenced by environmental factors such as oxygen availability, temperature fluctuations, extreme radiations, etc. These breathing cycles include ventilation, respiration, transport of gases (oxygen and carbon dioxide), and internal and cellular respiration. Amongst the four activities, environmental oxygen (at variable pressures) seems to influence/control inspiration, expiration, and end inspiration and end expiration. While highlanders are found to have a unique pattern of breathing under hypoxic conditions compensating for even chronic hypoxic conditions as a normal physiological process, lowlanders exposed to acute environmental conditions experience deleterious effects due to altered physiological parameters. To lowlanders, the time factor is the prime compensating factor in coping with altered environmental conditions in the early stages. Simple pranayama techniques can be beneficial as it controls the respiratory center, which eventually sets a quiet respiratory rhythm at around 2 seconds for inhalation and three seconds for exhalation and regulates the internal osmosis. These have a long-term compensatory role in regulating electrolyte and hormonal fluctuations, which might lead to the onset of pulmonary and cerebral edema. The author had led several Himalayan climbing expeditions up to 25000 feet and conducted cohort studies amongst low and high landers with and without pranayama and will share the data.

"While breathing is a key indicator of life, the breathing cycle is an indicator of health while irregular breathing confirms unhealthy conditions."
Thuppil Venkatesh

MONDAY

Biophysical effects of high altitude on the susceptibility of the living cells to corona virus infection

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The atomic and molecular structure and dynamics of living cells and microorganisms that function in a medium of about 70% water is susceptible to the pressure applied to their medium. The air pressure at sea level, (100kPa, 760mmHg) drops to about half of its value at about 5000m altitudes where people live in cities like La Rinconada (5,100 m) in Peru with about 50,000 inhabitants.
Water molecules act as clothes for biological molecules whose proper function is fulfilled in a unique hydrated state, in water medium. Water dynamics with a relaxation time of femtoseconds is vital for proper motions in macromolecules and its short life K, D and M structures as well as ice like transitional clusters that forms non-homogeneous high and low density liquid is required to stabilize molecular structures. Furthermore, the dielectric values of water (78-80) as well as its surface tension in the presence of specific ionic strength form the proper bioelectric and bioelectronic platform required for polyelectrolyte macromolecules activity. All of the above-mentioned roles of the water medium are deviated at different pressure to some extent.
Accordingly, the structure and integrity of SARS-CoV-2 corona virus, with a cell like structure consisting of protein embedded membrane lipid bilayer that encapsulates nucleic acid and proteins floating in water medium in a hydrated state can be effected by the medium pressure. On the other hand, the normal status of type II alveolar epithelial cells of the lung open system to atmosphere is also susceptible to the air pressure and the structure and dynamic of its ACE-2 receptors that anchor the Spike protein of the virus can be changed at different altitudes. Consequently, one can expect membrane status and its constituent molecules in both virus and target lung cells are changed at different altitudes, forming corresponding biophysical interactions.
The biophysical consequence of changes in air pressure, atmospheric different gas concentration including Oxygen on the molecular structure, dynamic and electrostatic interactions occurring between corona virus and target alveoli cells are addressed here and their ultimate effects on the viral infectivity will be discussed.
Keywords: Biophysics, altitude, air pressure, atmospheric gas concentration and density, bioelectric and bioelectronics of infectivity, corona virus

MONDAY

COVID-19 lower Case Fatality Rate in the high altitudes cities of Bolivia, Colombia, Ecuador, Mexico, and Peru: Possible physiological and environmental causes

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The COVID-19 worldwide public health breakout resulted in a historical research race. Medical research and practice at high altitude provided us with a unique perspective for the understanding of hypoxia in this disease. Popular belief stated that living under chronic hypobaric hypoxia would be correlated with higher COVID-19 severity. Previous studies from our team and others suggested a lower COVID-19 incidence in high altitude populations. Later, mortality became the focus of analysis. An analytic, retrospective, comparative multi-national study was carried out from the beginning of the pandemic until the end of 2020. Official open sources from Bolivia, Peru, Colombia, Ecuador, and Mexico were used to access the COVID-19 Case Fatality Rate (CFR) difference between the highland municipalities (or sample) (>2,500 m) compared to the lowland municipalities (or control) (< 1,000 m) in each country. Data analysis included statistical tables regarding the population, total positive cases, recovered cases, and deaths. Chi-square test, Odds ratio, Spearman correlations, and Post Hoc analysis were performed. Lower CFR was statistically significant in the highlands compared to the lowlands in all countries. The possible explanations that could explain this COVID-19 protective behavior at high altitudes are physiologic and environmental (physics). The physiologic include higher hemoglobin levels, erythropoietin levels, greater immunity, lower carbon dioxide levels, lower incidence of asthma, and a lower number of ACE2 receptors in high-altitude inhabitants. The environmental include higher Ultra-Violet radiation, lower molecular density in the atmosphere, and lower humidity.

MONDAY

Altitude promotes better survival rates in critically-ill obese patients with COVID-19

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BACKGROUND
Obesity, related to major risk factors for disease severity and mortality in COVID-19, is the most common chronic comorbidity in this disease. Although COVID-19 at high altitude seems to be associated with higher ICU discharge and hospital survival than at sea-level, high altitude is also associated with higher immune levels and inflammation. The survival rate of critically-ill obese patients with COVID-19 at altitude in comparison with overweight and normal patients was studied.
METHODS
A retrospective cohort study on all critical COVID-19 patients hospitalized in the ICU from a hospital in Quito - Ecuador (2,850 m) from Apr 1, 2020 to Nov 1, 2021 was carried out. 3 groups (normal, overweight, and obese BMI ranges) were assessed. Risk and mortality predictive factors, mechanical ventilation setting, extubation rates, analytical parameters, and multivariate regression analysis were used.
RESULTS
72% of men and 28% of women were studied. 45% of the patients were obese and presented increased arterial hypertension (p= 0.018). Mortality in obese patients (31%) was lower in absolute terms (48% in normal weight and 40% in overweight). Mean APACHE II (X=16) and SOFA (X=7) at admission showed no significant differences between groups. Overweight and obese patients required more PEEP compared to normal-weight patients, p= 0.001, p= <0.001, and p= 0.001 respectively. In obese patients, plateau pressure and mechanical power were higher while extubation failure was lower. Higher hematocrit and hemoglobin values and lower IL-6 and LDH were also found. In the multivariate analysis, the OR of 0.48 in obesity (95% CI: 0.23-0.97) was protective for mortality compared to normal and overweight. As predictors for mortality, ferritin was an independent factor in normal and obese weights, NLR was significant in obesity, and age in the overweight.
CONCLUSIONS
This preliminary study suggests high altitude protection in critically-ill COVID-19 patients with obesity compared to the patients with other BMI at sea level.

MONDAY

Elevated Humoral Immune Response to SARS-CoV-2 at High Altitudes Revealed by an Anti-RBD ′In-House′ ELISA

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The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the Coronavirus Disease 2019 (COVID-19) pandemic has made the serological surveillance a crucial tool for designing public health guidelines. In this context, the lack of diagnostic kits in our region motivated us to design an ELISA test to detect antibodies against the receptor binding domain (RBD) of the SARS-CoV-2 Spike glycoprotein. A robust, sensitive, cost-effective, and on-demand test was developed and 758 individuals from Tucumán, Argentina who underwent COVID-19 were studied. Results obtained showed a low correlation between anti-RBD IgG antibodies compared to those induced by virus N protein. In addition, it was detected that only 19% of the individuals developed antibody titers sufficient to be considered plasma donors. No differences in anti-RBD IgG titers were found between women and men, nor between different age groups. Analyzing a group of inhabitants of Tafí del Valle, Tucumán (located at 2014 meters above mean sea level; masl), they presented significantly higher and more persistent anti-RBD titers than the population of San Miguel de Tucumán (400 masl). These findings evidence a higher antibody response against SARS-CoV-2 in high-altitude individuals, which adds further evidence on the effect of altitude on the interaction between this new coronavirus, the immune system, and the development of infection.

MONDAY

Low serum erythropoietin levels are associated with fatal COVID-19 cases at 4,150 meters above sea level

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Previous studies suggested that erythropoietin (EPO) may protect against severe COVID-19-induced injuries, ultimately preventing mortality. This hypothesis is based on the fact that, in addition to promoting the increase in red blood cells, EPO is an anti-inflammatory, anti-apoptotic and protective factor in several non-erythropoietic tissues. Furthermore, EPO promotes nitric oxide production in the hypoxic lung and stimulates ventilation by interacting with the respiratory centers of the brainstem. Given that EPO in the blood is increased at highaltitude, we evaluated the serum levels of EPO in critical patients with COVID-19 at “Hospital Agramont” in the city of El Alto (4150 masl) in Bolivia. A total of 16 patients, 15 men, one woman, with a mean age of 55.8 ± 8.49 years, admitted to the Intensive Care Unit were studied. All patients were permanent residents of El Alto, with no travel history below 3000 masl for at least one year. Blood samples were collected upon admission to the ICU. Serum EPO concentration was assessed using an ELISA kit, and a standard technique determined hemoglobin concentration. Only half of the observed patients survived the disease. Remarkably, fatal cases showed 2.5 times lower serum EPO than survivors (2.78 ± 0.8643 mU/mL vs 7.06 ± 2.713 mU/mL; $p = 0.0096$), and 1.24 times lower hemoglobin levels (13.96 ± 2.56 g/dL vs 17.41 ± 1.61 g/dL; $p = 0.0159$). While the number of cases evaluated in this work is low, our findings strongly warrant further investigation of EPO levels in COVID-19 patients at high and low altitudes. Our results also support the hypothesis that exogenous EPO administration could help critically ill COVID-19 patients overcome the disease.

MONDAY

The *"safety factors"* protecting against the development of lung edema; a functional interpretation of pulmonary hypertension

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Extravascular lung water is strictly controlled by "*safety factors*" protecting against the development of edema. Waning of these factors inevitably leads to lung edema. The physiological low microvascular permeability may be impaired by conditions causing damage to the macromolecular assembly of the interstitial matrix. These conditions include exercise, hypoxia exposure and, even more, exercise in hypoxia. In fact, the increase in cardiac output leads to increase in pulmonary arterial pressure, lung capillary recruitment, increase in capillary surface for fluid exchange and potential increase in capillary pressure that represents the most critical factor causing edema (4, 5). Previous data from the literature in exercising humans in hypoxia showed remarkable inter-individual differences concerning the increase in pulmonary artery pressure, as well as the efficiency of the oxygen uptake at lung level. The latter point was derived from the dispersion of the lung ventilation/perfusion ratio and the increase in alveolar-capillary gradient for oxygen. These events can actually be explained by water accumulation in the peri-bronchial and peri-microvascular interstitial spaces (6). Further, recent data in about 50% humans undergoing work in hypoxia showed a greater increase in extravascular water, greater vasoconstriction, pulmonary hypertension and slower kinetics of alveolar-capillary O_2 equilibration; these findings were explained hypothesizing a greater proneness to develop lung edema possibly reflecting higher inborn microvascular permeability relating with specific morpho-functional features of the air–blood barrier (1, 2 , 6, 9). It is noteworthy that at clinical level, pulmonary hypertension is observed in apparently quite different conditions such as idiopatic pulmonary fibrosis, COPD patients, pulmonary fibrosis, combined pulmonary fibrosis and emphysema (11). A basic, so far unanswered pathophysiological question, remains: why does pulmonary hypertension develop? As a possible answer, one can hypothesize a common pathophysiological interpretation considering that pulmonary hypertension reflects a remarkable pulmonary vasoconstriction as a defensive mechanism to avoid an increase in capillary pressure to face a relatively higher inborn microvascular permeability (6). The deposition of fibrosis can also be regarded as a long- term functional adaptive response to an inborn high microvascular permeability. The use of vasodilators to treat pulmonary hypertension should carefully balance the consequences of capillary recruitment and increase in capillary pressure with actual patient's level of microvascular permeability (physiologically very low but unlikely so in presence of pulmonary edema). There are reports of massive lung edema following administration of vasodilators (7). Further, one shall consider that drugs increasing blood fluidity and microvascular flow induce lung edema (8).

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MONDAY

Chronic Hypoxia: The optimal environment for space travel and human settlements in space

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Following the accident on Apolo1, with 100% oxygen in the cabin, all spaceships travel with a sea level pressure and 20.9% oxygen. The extravehicular activity requires lowering the pressures to 1/3 that of sea level (Mt. Everest pressure) and increasing the percentage of oxygen to simulate a sea level PIO2. It is a complex pressure change maneuver and time-consuming. Permanently reducing the cabin pressure would be a great advantage. A paper by NASA in 2013 proposed for the spaceflight environment: 8 psia / 32% O2 (reducing the sea level pressure, 14.7 psi / 20.9% O2, but increasing the fraction of oxygen to replicate the sea level PaO2). However, we question this proposal, as it is based on the fear of hypoxia. Our proposal back in 2007 suggested that space travel should take place in a hypobaric environment of 9.5 psi / 20.9% O2 (like in the city of La Paz-Bolivia (3,600m) [11,811ft]). The logic behind it is that at all altitudes on planet Earth, life thrives in 20.9% Oxygen and 79% Nitrogen. PaCO2 also needs to be considered. Physiologically, over 200 million inhabitants of high altitudes above 2,000m [6,561ft] have perfectly everyday lives. The astronauts could benefit from an Extra-Vehicular Activity (EVA) suit pressure of only 149 mmHg [2.8psi] (lighter, much more comfortable, and efficient spacesuits), and space travel anemia could be reduced. The preparation before space travel could be carried out by adapting and living in a high-altitude environment, preferably the city of La Paz (one of the seven marvel cities of the world). La Paz, and its neighboring city of El Alto, with their 2 million inhabitants, located between 3,100 and 4,100m of altitude, are the perfect comfortable, pleasant, full-of-resources environments for achieving an adaptation to chronic hypoxia for space travel. We consider chronic hypoxia a fundamental step in BioSpaceForming (Adaptation to life in space). As all living beings start to move out of Earth into space, they will have to change their biology and adapt to an upgraded and more resistant chronic hypoxia physiological condition.

TUESDAY

Sympathovagal imbalance drives the chronic sustained hypoxia induced impairment of glucose homeostasis in normobaric experimental rats. Role of L/N type calcium channel blocker (cilnidipine)

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Chronic hypoxia (CH) underlying chronic obstructive pulmonary disease (COPD) is likely to signal a repertoire of events leading to type 2 diabetes mellitus (T2DM) in normobaric inhabitants. This work was undertaken to delineate the link between hypoxia, sympathovagal balance and glucose homeostasis (GH). We also assessed if cilnidipine, a dual L/N type calcium channel blocker can alleviate chronic hypoxia induced altered sympathovagal balance in turn impacting the glucose regulatory mechanisms. Wister strain albino rats were assigned to four groups: Group I: control, (normobaric normoxia, 21% O_2); group II: chronic hypoxia (CH) (normobaric 10% O_2, 90% N for 28 days); group III: normoxia+cilnidipine (cil, 2mg/kg/day); group IV: CH+Cil (normobaric 10% O_2, 90% N + cil, 2mg/kg/day). Sympathovagal balance was assessed by heart rate variability (HRV) analysis. Glucose homeostasis was evaluated by fasting plasma glucose (FPG), fasting plasma insulin, oral glucose tolerance test (OGTT), and HOMA-IR. Fasting lipid profiles were also assessed. Chronic hypoxia increased LF (nu), LF/HF and decreased HF (nu) in experimental rats. Additionally, CH increased FPG and HOMA-IR that were positively correlated with LF/HF, and induced an atherogenic lipid profile. OGTT revealed normal 2h post-challenge glucose levels. In cilnidipine treated normobaric chronic hypoxia exposed group, LF (nu), HF (nu) and LF/HF were lower compared to chronic hypoxia and glucose homeostasis parameters were comparable to control. Chronic hypoxia disrupts glucose homeostasis inducing isolated impaired fasting glycemia (i-IFG), a prediabetic state with sympathetic hyperactivity underlying its pathogenesis in experimental rats. Cilnidipine improved glucose homeostasis in chronic hypoxia by ameliorating sympathetic hyperactivity with complementary effects on lipid profile implying its use as an additional therapy against chronic hypoxia induced T2DM.

TUESDAY

Chronic hypoxia triggers mitochondrial plasticity in the brain of mice, but not in rats

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Adaptation to high altitude (HA) relies on adjustments of cellular metabolism that optimize O2 use and energy production. In tissues that have high energy demand and almost exclusive reliance on aerobic metabolism such as the brain, chronic hypoxia is a particularly strong stressor, however, strategies to adjust metabolic pathways for successful HA adaptation remain poorly understood. Compared to SD rats, FVB mice show successful adaptation to HA, we, therefore, used this model to investigate metabolic adjustments in the retrosplenial cortex (a key area involved in spatial learning, navigation, and self and external referencing) before or after exposure to chronic hypoxia (12% O2 – 21 days). We measured simultaneously the rates of O2 consumption and ATP production (JO2 - JATP) under conditions of oxidative phosphorylation in fresh permeabilized brain samples by coupled high-resolution respirometry and fluorometry (OROBOROS O2k). Using frozen samples, we then measured citrate synthase activity as an index of mitochondrial content, and the activity of enzymes representative of the glycolytic (hexokinase), aerobic (pyruvate dehydrogenase), and anaerobic (lactate dehydrogenase) metabolism.

Chronic hypoxia significantly increases JATP in mice (+132%) and to a lower extent in rats (+35%). In mice, this occurs in parallel with a reduction of JO2 (-28%), and a three-fold increase in the P/O ratio (JATP per atomic oxygen consumed) and without alterations in mitochondrial content. In rats, on the other hand, JO2 remains unchanged despite a six-fold increase in mitochondrial content. Activities of glycolytic, aerobic, or anaerobic enzymes are not altered after chronic hypoxia in both species. Our results show that chronic hypoxia optimizes the efficiency of mitochondrial JATP in the retrosplenial cortex of mice. Contrastingly, rats maintain JATP only by increasing mitochondrial content, hence a greatly reduced JO2 and JATP, when normalized to mitochondrial content, suggests drastic mitochondrial malfunctions.

We propose that in mice the reduced JO2 may ensure a broader and homogeneous O2 diffusion through the brain tissue and help prevent hypoxia at the subcellular level, while at the same time preserving (or even increasing) the necessary supply of ATP. One may speculate that the absence of such adjustments in rats may lead to defects in spatial cognition and memory, features that are key for biological fitness. This may explain, at least in part, the absence of common rats in high-altitude environments, where house mice thrive.

TUESDAY

Postnatal hypoxia alters mitochondrial oxygen consumption and affinity in mice, but not in rats.

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Hypoxic exposure during postnatal development induces delay of body growth and can lead to specific metabolic alterations. While species living at high altitude (HA) have metabolic adaptations to ensure adequate homeostasis, the effect of postnatal hypoxia remains poorly understood across species with different capacity to sustain hypoxia and adapt to HA. Compared to SD rats, FVB mice are a convenient model of successful HA adaptation, and we recently provided evidence suggesting that plasticity of mitochondrial functions under hypoxic conditions is an important feature of HA adaptation in mice. Therefore, we used this model to assess the effects of postnatal hypoxia on mitochondrial O2 consumption (OCR) and affinity (P50) in brain cortex (retrosplenial & V2 cortex). SD rats and FVB mice pups were born in normoxia and litters were exposed to normoxia or hypoxia (13.5% O2 – equivalent to an altitude of 3500m). At postnatal day 7 (P7), P14 and P21, mitochondrial O2 consumption was measured under (i) leak, (ii) oxidative phosphorylation with complexes I (CI) and II (CII) triggered independently or combined and (iii) CIV activation. Once CI and CII were active, we performed an aerobic-anoxic transition by allowing complete depletion of O2 in the recording chamber. We used the low-oxygen range of the oxygen consumption curve to calculate the affinity constant P50 (partial pressure of oxygen needed to reach half of the maximum O2 flux) and Vmax (maximum O2 flux). In normoxia, rats and mice OCR increased gradually in all states between P7 and P21 with mice showing higher values than rats. Postnatal hypoxia in mice induced a faster maturation of mitochondrial OCR, while there was no effect in rats. During postnatal development the mitochondrial electron transport chain in the brain of mice have a lower affinity (higher P50) for O2 than rats, which was further reduced at P14 when exposed to postnatal hypoxia. These results showed different responses to postnatal hypoxia between rats and mice that could be linked to their abilities to adapt to HA.

TUESDAY

Metabolic responses to intermittent hypoxia are modulated by sex hormones in male and female mice

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Intermittent hypoxia (IH) increases sympathetic nervous system activity, leading to altered glucose homeostasis, likely contributing to metabolic disorders in sleep apnea patients. While clinical studies have shown sex-specific associations between SA and metabolic disorders, we still need to understand how sex and sex-hormones alter the effects of IH on glucose homeostasis. We assessed whether metabolic effects of IH are modulated by sex and sex-hormones. Intact or gonadectomized male or female mice have been exposed to normoxia or IH (12h/day, 6% O2) at a moderate frequency (10 cycles/h) and we assessed plasma glucose and insulin levels, as well as insulin resistance and glucose tolerance under fasting (6h) or post-prandial conditions (12h fasting + 2h feeding). The roles of estradiol and estradiol receptor α (ERα) during IH exposures were assessed in gonadectomized females with estradiol supplementation and in ERαKO mice. In intact and gonadectomized male mice, skeletal muscles and liver were used to measure activity of antioxidant enzyme (SOD) in cytosol and mitochondrial extracts. IH improves glucose homeostasis in males. In females, gonadectomy induces insulin resistance in normoxia and this was prevented by estradiol and IH. Sex-specific effects were present in wild-type but not in ERαKO mice, showing that ERα establishes sex-specific metabolic responses to IH. In gonadectomized male mice under postprandial conditions, IH increases insulin levels and reduced SOD activities in the liver and gastrocnemius muscle. We conclude that sex and sex hormones modulate metabolic responses to IH in male and female mice, with contributions from testosterone and estradiol.

TUESDAY

Technical adjustments for reliable assessment of mitochondrial COX complex activity in liver samples of rats exposed to chronic hypoxia

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The mitochondrial complex IV (COX-Cytochrome c Oxidase) is the regulatory center for mitochondrial oxidative phosphorylation in which there is a transfer of electrons to dioxygen (O2) that will be reduced to water in a highly exergonic reaction. One of the most commonly used quantitative analyses for COX activity is the high-resolution respirometry technique of the O2K Oxygraph (OROBOROS) instrument. To do so, saponin-permeabilized samples are supplemented with the electron donor N,N,N′,N′-Tetramethyl-p-phenylenediamine dihydrochloride (TMPD) and ascorbate (TMPD autoxidation preventer) in a reoxygenated mitochondrial respiration medium (MIR05). Finally, sodium azide is used to inhibit COX. However, many questions regarding this procedure arise when mitochondria from cells and animals are exposed to chronic hypoxia. Indeed, chronic hypoxia has been suggested to alter COX enzyme kinetics, suggesting that a readjustment of this technique is required. To shed light on this problem, we used liver samples from Sprague Dawley rats maintained in normoxia and exposed to 12% hypoxia for 21 days. Three factors that may affect the measurement of COX activity were evaluated: ascorbate concentration, TMPD concentration, and the effect of MIR05 reoxygenation. The Design of Experiments (DoE) statistical approach was used to analyze the data. Our results showed that while ascorbate concentration does not affect the COX activity, TMPD concentration and MIR05 reoxygenation do. Indeed, compared to normoxic samples that required 1.9 mM TMPD to reach maximal stable activity, hypoxic samples demanded 1.6 mM TMPD. For both conditions, lower concentrations resulted in reduced activity, and higher concentrations resulted in unstable activities. In addition, reoxygenation of the MIR05 during measurement of COX activity erroneously reduced oxygen consumption values. We conclude that to perform a reliable measurement of COX activity in samples exposed to hypoxia, it is of utmost importance to avoid reoxygenation of MIR05 once the experiment has started. Furthermore, our results suggest that the optimal concentration of TMPD that allows assessment of maximal COX activity may depend on the type of tissue and the time of exposure to hypoxia conditions.

TUESDAY

A nanocurcumin and pyrroloquinoline quinone formulation averts soleus muscle atrophy under hypobaric hypoxia

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Hypobaric hypoxia (HH) is associated with various adverse effects in skeletal muscle, particularly muscle atrophy. An indigenously developed nanocurcumin formulation (NCF, patent no. 302877), prepared by combining the nanocurcumin (NC) and pyrroloquinoline quinone (PQQ), and has proven its protective role in cardiomyocyte adaptation to simulated high altitude. Therefore, it was hypothesized that the supplementation of NCF could prevent skeletal muscle from hypobaric hypoxia-induced oxidative injury and muscle wasting. Adult Sprague-Dawley male rats (210 ± 20 g) were issued from animal facility and divided into 5 groups (n= 6): normoxia control, hypoxia control, hypoxia + NCF, hypoxia + NC and hypoxia + PQQ. All the animals (except normoxia) were subjected to a decompression chamber at a temperature 22 ± 2 ºC humidity 50 ± 5 %, altitude 25,000 ft for 1, 3 or 7 days respectively. After HH-exposure, soleus muscle was removed from animal's hindlimb for further analysis. Progressively increasing hypobaric hypoxia exposure decreased relative muscle weight (0.063±0.005 vs 0.113 ±0.004 in gram) and with concomitant increased free radical generation ($p>0.01$, 1.4-fold) by day 7, of HH-exposure. Furthermore, oxidative muscle damage was observed significantly ($p>0.01$) by estimating the level of creatine phosphokinase, lipid peroxidation and protein carbonylation in soleus muscle after being subjected to HH exposure. We have found an increased muscle atrophic marker MuRF-1 ($p < 0.01$) expression and calpain activation (0.44 ± 0.03 vs 0.12 ± 0.021) by day 7, in soleus muscle. Importantly, NCF supplementation showed ($p \leq 0.05$) an improvement in skeletal muscle adaptation through effective alleviation of oxidative muscle injury, calpain activity and atrophic markers against simulated high altitude when compared to hypoxia control. NCF averts muscle wasting and maintains muscle morphology by restoring relative muscle weight and fiber cross-sectional area against hypoxic stress. To conclude, NCF-mediated anti-oxidative, anti-inflammatory effects lead to decreased proteolysis resulting in mitigated skeletal muscle atrophy under hypobaric hypoxia.

TUESDAY

MicroRNA is associated with cardiac dysfunction in diabetes mellitus

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MicroRNAs are altered and play one of crucial roles in physiological and pathological conditions, including diabetes mellitus. It was reported recently about phenomenon of hypoxia-induced miRNAs ("hypoxamiRs"), a specific subset of microRNAs. They are supposed to be regulated by hypoxia conditions and fine-tune cellular adaptation to hypoxia. Our study aimed to reveal microRNAs (hypoxamiRs) alterations in diabetic myocardium and during hypoxia. Methods: type II diabetes mellitus was induced in adult male Wistar rats with high-fat diet and low dose of streptozotocin. A group of animals were subjected to interval hypoxia trainings by “lifting” in barochamber on 3500 meters. MicroRNAs were measured using PCR technique, all results were analyzed statistically via SPSS program. Results: interval hypoxia trainings downregulated microRNA-1 in control rats. In diabetic animals the hypoxia effect was divergent: microRNA-320 expression was lowered, while microRNA-1 was elevated. Conclusions: hypoxia is a powerful stimulus affecting the expression of hypoxamiRs (microRNA-1, microRNA-320) in diabetic myocardium. Interestingly, each hypoxamiR concomitantly regulate expression of several target genes in order to accurately adjust the adaptive response of cells to hypoxia. These miRNAs are a part of complex molecular mechanisms involved in various hypoxia-associated biological processes in the heart.

TUESDAY

Trombosis venosa cerebral con transformacion hemorragica a los 6050 msnm en el cerro aconcagua- mal agudo de montaña

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Introducción:
La trombosis venosa cerebral es infrecuente. Los factores de riesgo son embarazo, puerperio, anticonceptivos orales, trombofilias, neoplasias. Rara vez se han reportado en el contexto de mal agudo de montaña. Siendo la cefalea, convulsiones y déficit focales los principales síntomas. El tratamiento de elección es la anticoagulación.

Reporte de caso:
Mujer de 23 años, indonesa, bilingue, sin antecedentes, a los 6050 msmn comienza con cefalea intensa, vértigo, afasia global, ataxia, desaturacion de O2 a 42 %. Desciende a 5050msnm por sus propios medios, constatándose fatiga extrema, deshidratación severa, mal agudo de montaña severo, al examen hipersomnia, afasia global y ataxia de 4 miembros, desaturacion de oxigeno 62% que mejora con oxigenoterapia, no evacuándose por razones climáticas, se inicia hidratación y corticoterapia ; horas posteriores presenta deterioro de conciencia, al arribo del hospital (700 msnm) se encontro hipersomne, mejoría de la afasia, responde y contesta en su idioma nativo, hemianopsia homónima, sin ataxia.

Resultados:
En RMN de cerebro con GD y angiorresonancia de vasos cerebrales se visualiza una lesión hipointensidad en T1 e hiperintensidad en T2 y FLAIR corticobsubcortical temporooccipital isquierdo, sin realce con gd. Cambios de señal con restricción de la difusion y caida del mapa de ADC a nivel del cuerpo calloso y corona radiata. Ausencia de vacio de flujo yugular interna y seno trasverso izquierdo. Estudios de trombofilia, inmunologicos, ecocardiograma y ecodopler de vasos del cuello negativos.

Conclusiones:
La complicación mas temida del mal agudo de montaña es el edema cerebral por altitud (0,5-1 %). El edema de cerebro conduciría a hipertensión endocraneana, la deshidratación y la poliglobulia fisiológica favorecería el estasis venoso, con el colapso del retorno venosos y posterior trombosis de senos venosos cerebrales. En nuestro caso a pesar del descenso y el tratamiento oportuno debe sospecharse dicha complicación al no mejorar la clínica.

TUESDAY

Escaladores sanos con lesión axonal periférica por altitud determinada por estudios de neuroconducción.

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Introducción. Los escaladores presentan signos y síntomas asociados a déficit sensitivo y motor en extremidades, sin lesiones tisulares visibles. A grandes alturas, el organismo genera una poliglobulia fisiológica, la cual en ocasiones puede asociarse a deshidratación, problemas nutricionales, vasoconstricción por frío y baja disponibilidad de oxígeno, que pueden ocasionar isquemia de los nervios.
Objetivos. El objetivo del estudio fue determinar la presencia o no de lesión de nervios periféricos en personas expuestas a hipoxia de altura a través de estudios de neuroconducción motora en miembros superiores e inferiores en el Cerro Aconcagua, Mendoza, Argentina.
Material y métodos. Se realizó un análisis transversal, descriptivo, observacional y correlacional, de personas expuestas a la hipoxia relacionada al ascenso de Cerro Aconcagua en enero de 2020. Se excluyeron personas que no completaron el estudio, con patologías preexistentes o neuropatía previa, escaladores sin plan de ascenso adecuado o tratamiento previo por MAM. Participaron personal de la patrulla de rescate, que mantienen un régimen de 14 días en altura/14 días en llano y escaladores que permanecieron en el cerro 14 ± 3 días.
Se realizó anamnesis de neuropatía, examen neurológico, medición de parámetros vitales, y estudio de neuroconducción motora de nervios cubitales, medianos, y tibiales posteriores, al iniciar la expedición y finalizar la misma, siendo estas determinaciones llevadas a cabo a los 3430 msnm.
Resultados. De los 87 participantes 44 fueron excluidos. La edad media de los 43 restantes fue de 39,8±5,5 (media±DS). La altura media alcanzada fue de 5959±1136msnm (media±DS). En relación a los nervios explorados se evidenció diferencias significativas pre y post-ascenso en las latencias y amplitudes distales y proximales de los nervios motores explorados ($p< 0,01$), no evidenciándose diferencias significativas en las velocidades de conducción pre y post-ascenso ($p=0,610$). Asimismo, no se observaron diferencias entre los nervios derechos e izquierdos ($p= 0,83$).
Conclusiones. La hipoxia de altura que presentaron los participantes determinó daño axonal de nervios periféricos, cuestión que puede asociarse a los factores de riesgo nombrados anteriormente y estudios controlados donde se puedan excluir estar variables pueden ayudar a aclarar la etiopatogenia del fenómeno y de esa manera poder tomar medidas para evitar daños crónicos e irreversibles.

TUESDAY

Mitochondrial responses to HIF-1 and acute hypoxia might underlie adaptation to high altitude in mice.

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Cellular and molecular responses to hypoxia have been optimized in several species living at high altitude. Mice (Mus musculus) have successfully colonized high altitude regions of south America in a short time frame after migration with the European invaders. Furthermore, they have a phylogeographical origin close to the Himalayan mountains, accordingly, we hypothesized that they carry traits of pre-adaptation to hypoxia. In line with this hypothesis, we previously reported that the expression of HIF-1α in the brain is higher in mice than in rats under acute hypoxia. HIF-1 is a transcription factor that regulates cellular metabolism by reducing the mitochondrial O2 consumption in hypoxia. We therefore thought to assess whether mitochondrial functions differ between rats and mice under normoxic conditions, and in response to acute hypoxia or pharmacological stabilization of HIF-1α. We used adult male FVB mice and SD rats exposed for 6 hours in normoxia (21% O2), hypoxia (10% O2 - equivalent to an altitude of 5000m) or normoxia with injection of deferoxamine (DEF - 200mg/kg), an iron chelator that stabilizes HIF-1α. Then we used liver and brain cortex to measure mitochondrial O2 consumption rates (OCR) under conditions of (i) proton leak, (ii) oxidative phosphorylation (OXPHOS) with complex I and II triggered independently or combined, (iii) maximal activity of the electron transfer chain (ETC) and (iv) activation of complex IV. In both tissues, mice had higher OCR under leak, OXPHOS and ETC. In contrast, CIV activity was higher only in the liver, suggesting higher mitochondrial mass, while structural changes of the ETC likely underlie differences in the brain cortex. Hypoxia and DEF decreased OCR only in the liver of mice under all conditions except under CIV activation. These results strongly suggests that the HIF pathway plays a more prominent role to adjust cellular metabolism and could contribute to high altitude adaptation in mice.

WEDNESDAY

The dysfunction of Na/K pump driving water efflux from the cells as a primary mechanism for cell pathology

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The metabolic control of cell hydration is a quantum-sensitive fundamental cell parameter determining cell membrane functional activity. The cell membrane is a highly permeable to water, however because of metabolic formation of endogenous water molecules during intracellular oxidation, the pumping from the cells generates osmotic gradient on cell membrane. In animal cells, the electrogenic Na/K pump is a central metabolic mechanism controlling the osmotic gradient on membrane, which is realized by its stoichiometry and activation of intracellular oxidative-phosphorylation process accompanied by the formation of endogenous water molecules. Two quantum-sensitive cell membrane mechanisms are discovered through which the intracellular Ca ($[Ca]_i$)-dependent control of the Na/K pump activity is realized. They are: a) cGMP-dependent Ca efflux from the cell and b) cAMP-dependent R Na/Ca exchange, which are activated by (10^{-11}-10^{-10}M and 10^{-9}-10^{-8}M) ouabain receptors in cell membrane, respectively. Both families of receptors, having non-canonic ouabain receptor functions, serve as targets through which the biological effects of quantum-mechanical signals on cells are realized. Studies on perfused squid axons and intact snail neurons have shown that transmembrane water fluxes activate ionic currents having the same direction and inactivate those having opposite direction. Therefore, it was elucidated that the Na/K pump driving water efflux is a key metabolic mechanism controlling semipermeable properties of cell membrane, the dysfunction of which is a common consequence of cell pathology and generation of pain in neuromuscular systems. The lecture will demonstrate the experimental data on the dysfunction of quantum-sensitive cGMP-dependent Ca-efflux from the cells-leading to Na/K pump inhibition, which is a primary mechanism of cell pathology.

WEDNESDAY

HIF-1 mediated activation of antimicrobial peptide LL-37 in type 2 diabetic patients

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Infections are common in patients with diabetes, but increasing antibiotic resistance hampers successful bacterial clearance and calls for alternative treatment strategies. Hypoxia-inducible factor 1 (HIF-1) is known to influence the innate immune defense and could therefore serve as a possible target. However, the impact of high glucose on HIF-1 has received little attention and merits closer investigation. Here, we show that higher levels of proinflammatory cytokines and CAMP, encoding for the antimicrobial peptide cathelicidin, LL-37, correlate with HIF-1 in type 2 diabetic patients. Chemical activation of HIF-1 further enhanced LL-37, IL-1β, and IL-8 in human uroepithelial cells exposed to high glucose. Moreover, HIF-1 activation of transurethrally infected diabetic mice resulted in lower bacterial load. Drugs activating HIF-1 could therefore in the future potentially have a therapeutic role in clearing bacteria in diabetic patients with infections where antibiotic treatment failed.

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WEDNESDAY

Erythropoietin receptor regulates tumor mitochondrial biogenesis through iNOS and pAKT

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Erythropoietin receptor (EPOR) is widely expressed in healthy and malignant tissues. In certain malignancies, EPOR stimulates tumor growth. In healthy tissues, EPOR controls processes other than erythropoiesis, including mitochondrial metabolism. We hypothesized that EPOR also controls the mitochondrial metabolism in cancer cells. To test this hypothesis, we generated EPOR-knockdown cancer cells to grow tumor xenografts in mice and analyzed tumor cellular respiration *via* high-resolution respirometry. Furthermore, we analyzed cellular respiratory control, mitochondrial content, and regulators of mitochondrial biogenesis *in vivo* and *in vitro* in different cancer cell lines. Our results show that EPOR controls tumor growth and mitochondrial biogenesis in tumors by controlling the levels of both, pAKT and inducible NO synthase (iNOS). Furthermore, we observed that the expression of EPOR is associated with the expression of the mitochondrial marker VDAC1 in tissue arrays of lung cancer patients, suggesting that EPOR indeed helps to regulate mitochondrial biogenesis in tumors of cancer patients. Thus, our data imply that EPOR not only stimulates tumor growth but also regulates tumor metabolism and is a target for direct intervention against progression.
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WEDNESDAY

What has erythropoietin to do with chronic mountain sickness?

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Decrease in the number of red blood cells (anemia), linked (or not) to a reduced level of erythropoietin (EPO) in the plasma, leads to fatigue, weakness, and shortness of breath. Conversely, an overproduction of red blood cells, as occurs in doping, linked to exogenous administration of EPO, is associated with an increased oxygenation capacity in the blood and greater physical endurance. At altitude, poly-erythrocythemia (also called chronic mountain sickness - CMS), which is an "excessive" increase in red blood cells, paradoxically leads to fatigue, weakness, and shortness of breath. In this work we investigate the possible physiological causes why, despite the increase in EPO (and red blood cells) in the CMS, decrease in ventilation occurs. We evaluated in mouse models with cerebral or plasma EPO overexpression, how this increase acts in the brainstem (center of ventilation control), and in the carotid bodies (CB - peripheral sensors of pH, oxygen, and CO2). The results showed that central EPO overexpression stimulates hypoxic ventilation in the brainstem through interaction with the respiratory centers. However, peripheral EPO overexpression inhibits ventilation, most likely through interaction with CB. To further understand how EPO interacts with CB under hypoxia, we used "*en bloc*" preparations containing the carotid sinus nerve (CSN) from adult male rats (Sprague Dawley). Our results showed an inverted U dose response of CSN to EPO. EPO acts as a stimulator of CSN activity in response to hypoxia at concentrations below 0.5 IU/ml, whereas EPO concentrations above 0.5 IU/ml decrease the CSN response to hypoxia reaching complete inhibition at 2 IU/ml. We evaluated whether the inhibition of high doses of EPO on the activity of CSN could be due to an increase in the production of nitric oxide (NO). For this, the CB preparations were incubated with 2 IU/ml of EPO and a non-specific inhibitor of NO synthase (L-NAME) or a specific neuronal NO synthase inhibitor (7NI). Both NO inhibitors completely restored CSN activity in response to hypoxia. Considering that NO is an inhibitory competitor of oxygen in mitochondrial complex IV, we conclude that increased plasma levels of EPO could trigger chronic mountain sickness in individuals with abnormal production of NO, or dysfunction of mitochondrial complex IV in CB.

WEDNESDAY

PULMONARY ARTERIAL PRESSURE AT REST AND DURING EXERCISE IN CHRONIC MOUNTAIN SICKNESS

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More than 40 million people are living at high altitude worldwide. An increase of pulmonary artery pressure (PAP) is a hallmark of high-altitude exposure and, if pronounced, may be associated with important morbidity and mortality. Up to 10% of this population suffer from chronic mountain sickness (CMS), which is a debilitating problem. In these patients increased (PAP), may contribute to exercise intolerance and right heart failure. Surprisingly, there is little information on the usual PAP in high-altitude populations and CMS patients.

We, therefore, conducted two systematic reviews (MEDLINE and EMBASE) and meta-analysis of studies published (in English or Spanish) on echocardiographic estimations of PAP and measurements of arterial oxygen saturation: **1)** between 2000 and 2015 in apparently healthy participants at high-altitude and low altitude. Twelve high-altitude studies comprising 834 participants and 18 low-altitude studies (710 participants) fulfilled the inclusion criteria. The combined mean systolic PAP (right ventricular-to-right atrial pressure gradient) at high altitude [25.3 mmHg, 95% confidence interval (CI) 24.0, 26.7], as expected was significantly ($P < 0.001$) higher than at low altitude (18.4 mmHg, 95% CI 17.1,19.7), and arterial oxygen saturation was significantly lower (90.4%, 95% CI 89.3, 91.5) than at low altitude (98.1%; 95% CI 97.7, 98.4). **2)** the second systematic review and meta analysis was until 2018 in CMS patients at rest and during mild exercise. Nine studies comprising 287 participants fulfilled the inclusion criteria. At rest, the point estimate from meta-analysis of the mean systolic PAP was 27.9 mmHg (95% CI 26.3-29.6 mmHg). These values are 11% (+2.7 mmHg) higher than in apparently healthy high-altitude dwellers. During mild exercise (50 W) the difference in mean systolic PAP between patients and high-altitude dwellers was markedly more accentuated (48.3 *versus* 36.3 mmHg) than at rest.

These findings indicate that at an altitude where the very large majority of high-altitude populations are living, pulmonary hypertension appears to be rare. However this is not the case in CMS patients in which sPAP was markedly increased at rest, getting even higher during mild exercise, comparable with daily activities.

WEDNESDAY

Should Chronic Mountain Sickness patients (Poly-Erythrocythemia) be phlebotomized?
Se debería sangrar a los poliglobulicos?

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The oxygen transport triad clearly shows that when there is an insufficiency of the pneumo-dynamic pump or the hemo-dynamic pump, the increase of hemoglobin is the optimal, most energy-efficient mechanism for survival. Upon ascent to high altitude, both pumps work to compensate for the reduced pressure of oxygen. It has been estimated that it takes around 40 days to achieve a total elevation to the optimal hematocrit/hemoglobin after arrival at a fixed altitude like the city of La Paz, 3,500m. Analogously when the lungs suffer different pathologies and reduce the gas exchange areas at high altitude, a gradual increase of red blood cells is the optimal energy-saving mechanism for sufficient oxygen transport to the tissues and hence to mitochondria. Depending on the degree of respiratory insufficiency, the hematocrit can rise above the normal levels of permanent residents. This compensating mechanism is fundamental for survival at high altitude with respiratory, cardiac, or other organ pathologies. If these patients are phlebotomized, the perfect balance of the oxygen transport system is altered. This induces an increase in the work of the hemo-dynamic pump and pneumo-dynamic pumps. Unfortunately, it is misinterpreted as an improvement. There will again be a gradual hemoglobin increase, and a reduction of the work of the pneumo-dynamic and hemo-dynamic pumps, reaching optimal equilibrium once again. Consequently, these patients should not be bled but their original pathologies should be treated.

THURSDAY

Introducing the brain erythropoietin circle to explain adaptive brain hardware upgrade and improved performance

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Executive functions, learning, attention, and processing speed are imperative facets of cognitive performance, affected in neuropsychiatric patients. In clinical studies on different patient groups, recombinant human (rh) erythropoietin (EPO) revealed mighty, hematopoiesis-independent effects on neuroprotection/neuroregeneration and lastingly improved higher cognition and reduced brain matter loss. Correspondingly, rhEPO treatment of rodents or EPO receptor (EPOR) overexpression in pyramidal neurons caused remarkable, enduring cognitive improvement, together with enhanced hippocampal long-term potentiation. The 'brain hardware upgrade', underlying these observations, includes an EPO induced ~20% increase in pyramidal neurons and oligodendrocytes in cornu ammonis hippocampi in absence of elevated DNA synthesis. Simultaneously, EPO reduces microglia numbers and dampens their activity/metabolism as prerequisites for undisturbed EPO-driven differentiation of pre-existing local neuronal precursors. These processes depend on neuronal and microglial EPOR. This novel mechanism of powerful postnatal neurogenesis, outside the classical neurogenic niches, and swift *on-demand* delivery of new cells, paralleled by dendritic spine increase, let us hypothesize a physiological procognitive and performance-enhancing role of hypoxia-induced endogenous EPO in brain ('brain doping'), which we imitate by rhEPO treatment. Thus, the *brain EPO circle* emerges as model explaining adaptive 'brain hardware upgrade' and improved performance. In this fundamental regulatory circle, neuronal networks, challenged by motor-cognitive exercise, drift into transient 'functional hypoxia', thereby triggering neuronal EPO/EPOR expression. Notably, the brain EPO circle can be entered anywhere, starting either with mild to moderate inspiratory hypoxia, with rhEPO treatment or the aforementioned motor-cognitive challenge as inducer of functional hypoxia, leaving plenty of possible ways for future therapeutic interventions.

THURSDAY

Sexual dimorphism in the rodent brain metabolism at high altitude

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The brain is the largest consumer of energy in the body and provides a unique metabolic environment for diverse cell lineages. Metabolic sex dimorphism in the brain occurs in numerous cognitive and emotional disorders in which males are more affected by developmental-onset disorders and females by a higher frequency of adult-onset disorders. The exact mechanism of sex bias in brain diseases is fairly known, but it is likely to be induced by an interaction of hormonal and cellular differences in brain regions, resulting in differential responses to stress, such as hypoxia. At high altitude, low barometric pressure strains the oxygen supply and metabolic demands of the brain. Although reduced arterial oxygen uptake is restored by erythropoiesis, low arterial pressure can influence O2 diffusion from capillaries to cells, leading to alterations in the microvasculature and mitochondrial function. We previously demonstrated in adult male rats that brain microvasculature increases after acclimatization at high altitude (Jungfraujoch, 3450 masl), measured 11 days after ascent from Zurich (408 masl). The cerebral neovasculature is stimulated at high altitude, by both, vascular endothelial growth factor (VEGF), and by erythropoietin (EPO), a growth factor that exerts a sex-differentiated impact on mitochondrial respiration. In this work, we evaluated in rodents whether there is sexual dimorphism in mitochondrial respiration after acclimatization to high altitude. Using high-resolution respirometry (OROBOROS Oxygraph-2k), we evaluated how mitochondrial oxidative phosphorylation (OXPHOS) is affected during development (postnatal days (P) 7, 14 and 21) and adulthood (P90) in rats and mice acclimatized for generations (>30 years) at high altitude (e.g. in La Paz, Bolivia, 3600 masl) and compared the data to low altitude controls (Quebec, Canada, 98 masl). Two areas involved in spatial memory consolidation were analyzed: the hippocampus and the retrosplenial cortex. In rats kept either in La Paz or Quebec, no differences in mitochondrial function were observed in any of the areas. In contrast, in mice, the retrosplenial cortex showed greater mitochondrial respiration than the hippocampus from mice kept at low altitude. Mice kept in La Paz, however, increased leakage and decreased OXPHOS at P7 in males, remaining unchanged at the other ages tested. In contrast, in the hippocampus, female mice showed higher OXPHOS at P7 than males kept in Quebec. At high altitude, a general increase in mitochondrial function in the hippocampus was observed in both sexes at all ages, with females showing higher OXPHOS than males at P7 and P14; but later in development, equal higher levels were observed in both sexes. To test whether increased mitochondrial function during female hippocampal development is driven by estrogen signaling, we measured estrogen receptor □ (ER□) in the hippocampus at P7 and indeed observed higher expression in females. Accordingly, we conclude that the hippocampus is an area of sexual dimorphism and that females have a greater mitochondrial function at an earlier stage of postnatal development, regulated by estrogen signaling. These results could imply neuroprotection of females to brain stress caused by hypoxia at high altitude during early development.

THURSDAY

Neuroprotective effect of *Mucuna pruriens* derived β-Sitosterol preconditioning on cerebral ischemic rats

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Mucuna Pruriens has long been used in traditional Ayurvedic Indian medicine in an attempt to treat diseases including Parkinson disease. Although there is no such reports on *Mucuna Prueins* extracts in brain pathophysiology either in animals or human clinical trials hence this study was undertaken with an hypothesis that bioactive compound(s) of *Mucuna Pruriens* possibly protect cerebrovascular ischemia . To find out the outcome on this hypothesis, authors laboratory used *In Silico, In Vitro* and *In Vivo* procedures. Primary phytochemical analysis of seed extracts of *M.Pruriens* were done followed by *In Vitro* antioxidant studies too. Isolation and identification of bioactive compound(s) from *M. Pruriens* were done by using HPLCT. Further . assessment of binding activity of isolated bioactive compounds potential of the ligand, molecular docking and molecular dynamic study were also done. *Tau* and *NMDAR* were selected as brain target proteins in cerebral ischemia. Further *In Vivo* study on unilateral carotid artery occluded (75 minutes) rats preconditioned with specific bioactive compound(s) and whole extracts were done to evaluate mRNA expression of Tau and NMDAR proteins. Histopathology and neurological scores of post cerebral ischemic rats were evaluated. Results found that β-Sitosterol and L-DOPA were the most concentrated bioactive compounds in *M.Pruiens*. Detail results will be discussed during 8th Chronic Hypoxia Symposium.

THURSDAY

HDAC inhibition Prevent Hypobaric Hypoxia Induced Neurodegeneration and Memory Impairment

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Hypobaric hypoxia at higher altitudes usually impairs cognitive functions. Previous studies suggested that epigenetic modifications are the culprits for this condition. Here, we set out to determine, how hypobaric hypoxia mediates epigenetic modifications and how this condition worsens neurodegeneration and memory impair in rats. In the current study, different duration of hypobaric hypoxia exposure showed a discrete pattern of histone acetyltransferases and histone deacetylases (HDACs) gene expression in the hippocampus when compared with control rat brains. The level of acetylation sites in histone H2A, H3 and H4 was significantly decreased under hypobaric hypoxia exposure compared to the control rat's hippocampus. Additionally, inhibiting the HDAC family with sodium butyrate administration (1.2 g/kg body weight) attenuated neurodegeneration and memory loss in hypobaric hypoxia-exposed rats. Moreover, histone acetylation increased at the promoter regions of brain-derived neurotrophic factor (BDNF); thereby its protein expression was enhanced significantly in hypobaric hypoxia exposed rats treated with HDAC inhibitor compared with hypoxic rats. Thus, BDNF expression up regulated cAMP-response element binding protein (CREB) phasphorylation by stimulation of PI3K/GSK3β/CREB axis, which counteracts hypobaric hypoxia-induced spatial memory impairment. In conclusion, these results suggested that sodium butyrate is a novel therapeutic agent for the treatment of spatial memory loss associated with hypobaric hypoxia, and also further studies are warranted to explore specific HDAC inhibitors in this condition.

Keywords: brain-derived neurotrophic factor; histone acetyl transferases; histone deacetylase; hypobaric hypoxia.

THURSDAY

Effect of chronic hypoxia on epitranscriptomic machinery in the heart

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Ischemic heart disease is the leading cause of death worldwide. Cardiac tolerance to ischemia can be increased by adaptation to chronic hypoxia, which is associated with significant myocardial gene expression profile changes. Among the possible mechanisms of gene expression alterations are epigenetic modifications of RNA – epitranscriptomics. Our study focused on two of the most prominent marks – N^6-methyladenosine (m^6A) and N^6,2'-O-dimethyladenosine (m^6Am). We found that m^6Am is more abundant in rRNA-depleted RNA isolated from rat cardiomyocytes than m^6A. Hypoxic adaptation of rats affected the expression of m^6A and m^6Am regulators in the heart, including up-regulation of both demethylases – ALKBH5 (m^6A) and FTO (m^6Am and m^6A). Based on these results, we studied the effects of FTO (the only m^6Am eraser) inhibition on the proteome, metabolism, and also tolerance to oxygen deprivation of rat cardiomyocytes. FTO inhibition affected protein levels involved in crucial cellular processes such as gene expression, non-coding RNA processing, peptide biosynthesis, and cellular metabolism. Glycolytic and respiration rates of cardiomyocytes were increased after FTO inhibition. Most importantly, we found that FTO inhibition decreases the tolerance of cardiomyocytes to oxygen deprivation *in vitro*, supporting the possible role of epitranscriptomic regulations in the cardioprotective mechanisms.

THURSDAY

Vitamin D influences cardiovascular diseases – Role of VEGF

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Background:
Cardiovascular disease (CVD) is considered as the leading cause of disability and death. Epidemiological data in humans have shown that vitamin D insufficiency is associated with hypertension, left ventricular hypertrophy, increased arterial stiffness, and endothelial dysfunction. Vitamin D in relationship with vasculogenic protein like VEGF on CVD is yet to be ascertained. This study was aimed to assess the role of Vitamin D on CVD in the perspective of serum VEGF levels.
Methodology:
Cross sectional study was conducted on different types of CVD patients (age range: 40- 80 years) who were diagnosed for first time and admitted in ICCU. Routine physical anthropometry, hematology and serum biochemical pertaining to cardiac diseases were done. Serum VEGF and NOS3(e-NOS) were also evaluated by ELISA method for all the CVD patients (n=278). Statistical analysis of all the results were done by using SPSS-Version 23 software.
Results & Discussion:
Vitamin D levels of serum in all the CVD patients were found to be lowered. We found decreased VEGF and NOS3 levels in all groups of CVD patients. Decreased VEGF level indicate a possible decrease of vasculogenesis in myocardial and vascular tissues which indicates impaired cardiovascular defense mechanism against systemic insults. Decreased plasma NOS3 level in CVD patients may be due to the lower serum VEGF which acts as a NOS3 stimulant to produce NO. The study further shows a positive correlation (r = 0.20) between vitamin D and NOS3 which indicates a possible lower expression of VEGF protein and lack of cell signaling pathways for NOS3 expression. The present study established a link between vitamin D and VEGF, on cardiovascular pathophysiology of CVD.
Conclusion:
Deficiency of vitamin D leads to most of the CVD in present study possibly through reduced VEGF protein, vasculogenesis and cardiovascular remodeling.

Key words: cardiovascular disease, vitamin D, VEGF, NOS3

THURSDAY

Hypertension and myocardial infarction at high altitude, what is the truth??
¿Hipertensión e infarto de miocardio a gran altura, cual es la verdad??

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Se ha especulado durante mucho tiempo que las “grandes altitudes” en América, representarían una carga adicional para el trabajo cardiaco y las manifestaciones clínicas inherentes a la enfermedad cardiaca isquémica y a sus factores de riesgo, como la hipertensión arterial sistémica, por ejemplo.

Lo cierto es que, aunque efectivamente una buena parte de la población boliviana occidental reside a grandes altitudes, El Alto, por ejemplo, una ciudad y municipio de Bolivia, con una altitud promedio de 4.150 m s. n. m., ubicado en la provincia Pedro Domingo Murillo del departamento de La Paz, localizada al oeste del país en la meseta altiplánica y que es la ciudad más poblada del departamento y la segunda ciudad más poblada de Bolivia (la primera ciudad de mayor densidad poblacional es Santa Cruz de la Sierra, dejando a la ciudad de La Paz en tercer lugar) con casi un millón de habitantes – 943.558; muestra que epidemiológicamente se comporta de manera “estándar”, con una proporción de hipertensos aun inferior que La Paz, (14 % vs. 17%) y mucho menos que Santa Cruz (23 a 26% dependiendo de las series).

Los factores de riesgo, tan importantes en el mundo entero, tienen un sesgo casi cultural, el tabaquismo, presente sin duda, no tiene el impacto que se observa en países industrializados, la falta de actividad física y el sobrepeso y la obesidad, efectivamente se encuentra presente en mas del 50% de la población nacional, y con una distribución demográfica predominante en las clases de ingresos medios bajos.

La dieta saludable es excepcional debido a una tendencia franca al consumo de carbohidratos entremezclados entre sí (arroz, papa y fideo, en ocasiones los tres en el mismo plato), y aunque la dieta también incluye el consumo de granos integrales, legumbres, frutas y verduras totales, aun no se tiene el impacto de los frutos secos y semillas, predominando las bebidas azucaradas, la carne procesada y el sodio, cuya adición incluso al pan, no tiene reglamentación ni restricción alguna.

Sin embargo, OBSERVACIONALMENTE, se considera que el número de eventos cerebrovasculares en cualquiera de sus presentaciones, excede al diagnóstico de infarto agudo de miocardio, angina estable, inestable o cualquier equivalente isquémico; aunque efectivamente esto tiene un sesgo dependiente del grupo poblacional y su acceso a seguros de cobertura médica (mayor cantidad de eventos cardiacos en el seguro de la Caja Petrolera, la Banca privada, la Caja Nacional de Salud, etc., dejando al final al servicio público, con menos casos observados por no tener una población fija, sino migrante y variada.

Infelizmente, con el paso de los años y el advenimiento de los cambios de los estilos de vida y el aumento de la carga de estrés social, laboral e incluso familiar, se ha observado un crecimiento (gracias a Dios aun no exponencial) de los casos diagnosticados y corroborados como de enfermedad cardiaca coronaria.

Probablemente el curso natural de la industrialización y el progreso, jueguen en contra y añadan patología emergente a las enfermedades cardiacas que todavía son un desafío local, como la valvulopatía reumática, el corazón pulmonar crónico y las neumopatías crónicas responsables de su aparición (la tuberculosis aun presente endémicamente en la nación con presentaciones de pericarditis en todas sus variedades, -crónica productiva, exudativa y constrictiva por ejemplo), las cardiopatías congénitas de la infancia y la enfermedad de Chagas en todas sus formas; dilatada, arrítmica, isquémica, mixta o muerte súbita cardiaca.

THURSDAY

Comparison of cytokines levels among COVID-19 patients living at sea level and high altitude

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Background**:** At the end of 2019, a novel coronavirus denominated SARS-CoV-2 rapidly spread through the world causing the pandemic coronavirus disease known as COVID-19. The difference in the inflammatory response against SARS-CoV-2 infection among people living at different altitudes is a variable not yet studied.
Methods: A descriptive cross-sectional study was performed in two Peruvian cities at different altitudes for compari- son: Lima and Huaraz. Five important proinflammatory cytokines were measured including: IL-6, IL-2, IL-10, IFN-**γ** and TNF-α using ELISA assays.
Results: A total of 35 COVID-19 patients and 10 healthy subjects were recruited from each study site. The mean levels of IL-6 ($p < 0.03$) and TNF-α ($p < 0.01$) were significantly different among the study groups. In the case of IL-6, patients from Lima had a mean level of 16.2 pg/ml (healthy) and 48.3 pg/ml (COVID-19), meanwhile, patients from Huaraz had levels of 67.3 pg/ml (healthy) and 97.9 pg/ml (COVID-19). Regarding TNF-α, patients from Lima had a mean level of 25.9 pg/ml (healthy) and 61.6 pg/ml (COVID-19), meanwhile, patients from Huaraz had levels of 89.0 pg/ml (healthy) and 120.6 pg/ml (COVID-19). The levels of IL-2, IL-10 and IFN-γ were not significantly different in the study groups.
Conclusion: Patients with COVID-19 residing at high-altitude tend to have higher levels of inflammatory cytokines compared to patients living at sea level, particularly IL-6 and TNF-α. A better understanding of the inflammatory response in different populations can contribute to the implementation of therapeutic and preventive approaches. Further studies evaluating more patients, a greater variety of cytokines and their clinical impact are required.

FRIDAY

Hepatic mitochondrial metabolism is higher and develops earlier in high-altitude mice than in rats

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In high-altitude (HA) settings, well-acclimatized species have developed physiological and cellular mechanisms that allow them to maximize O_2 and energy use. These changes are particularly evident in highly metabolic organs such as the liver (≈50% of total metabolism in rodents). We have shown previously that adult FVB mice exhibit significantly higher hepatic mitochondrial respiration after 21 days of exposure to hypoxia (12% O_2 equivalent to 4300 masl) compared to SD rats. Moreover, it has been reported that permanent hypoxia promotes the upregulation of metabolic mechanisms. The establishment of such adaptive adjustments is of utmost importance during postnatal development due to the high energy requirements for the maturation of cellular and subcellular systems. Therefore, here we have evaluated the hepatic mitochondrial respiration during postnatal development and adulthood of FVB mice and SD rats established and living at 3600 masl over 50 generations.
The liver samples were obtained at postnatal ages P7, P14, P21, and P90. Using high-resolution respirometry (OROBOROS-O2K), we evaluated the mitochondrial O_2 consumption rate (OCR); the activated fraction of the electron transport chain (ETC) linked to NADH use (CI), succinate use (CII), or both (CI&CII).
Our results show an age-dependent increase in OCR during postnatal liver development in both species. However, mice show higher OCR values than rats at all tested ages, except P7. Furthermore, OCR in mice increases progressively from P7 to P14, peaking at P21 before stabilization in adulthood. In contrast, OCR in rats remains unchanged from P7 to P14, showing only a significant increase at P21, which is still below the levels reached in adulthood. In parallel, regardless of age, both species show greater involvement in the CII-linked pathway compared to the CI-linked pathway.
We conclude that mitochondrial respiration during postnatal development of the liver is higher in HA mice than in rats. Furthermore, the early OCR increase during mice development suggests a more rapid maturation of mitochondrial function when compared to rats. Noticeably, the increased CII mitochondrial activity compared to CI in both species agrees with previous reports claiming a pivotal role of succinate in the metabolic adaptation to hypoxia.

FRIDAY

The Norwegian Mountain Medical Society and Acid-Base at extreme altitudes

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First many thanks to my friend, Professor. Dr. Gustavo Zubieta-Calleja for the possibility of participating in the 8th Chronic Hypoxia Symposium Oct 2022. We met in Copenhagen when Gustavo was visiting professor in the medical faculty. We had many interesting meetings with prof. Poul-Erik Pavlev, the great Danish physiologist. I worked at the University Hospital in Oslo from 1962 to 2004. My specialty was: «Inorganic Clinical Biochemistry» with a focus on blood gases, acid-base, and electrolytes. I got much of my special education in blood gases and acid-base in Copenhagen with professor Poul Astrup and professor Ole Siggaard- Andersen being the teachers. That was in the 1970`s. Norway is a very mountainous country, in particular in the west and north regions. We have no peaks with altitudes more than 2469 meters above sea level. The state of readiness for help in our mountains is very high. This is due to: 1. Norwegian Red Cross Rescue Corps with 18000 members in more than 300 divisions with trained personnel in first aid. 2. Norwegian Society for Mountain medicine with central leaders for all relevant medical fields. The interest in high-altitude medicine is high in our country, so many Norwegians travel to Himalaya, Andes, Alaska, and other places with high mountains. In 1985, eleven Norwegians reached the summit of Mt. Everest. They did some research on water and electrolyte metabolism. Also, comparative physiology was of interest to the group. How can birds manage so well about 1000 meters above the summit? My presentation will be focused on history. I have not been much involved in lessons and other information on high-altitude medicine. In 1978 I gave a presentation in the International Federation of Clinical Biochemistry division pH and blood gases. My subject was the calculation of base excess in the four most used blood gas measuring instruments at that time: Corning, Radiometer, Instrumentation Laboratorium, and AVL. When Siggaard-Andersen published Base Excess, it was not accompanied by an algorithm for the calculation of BE. You had to use the Siggaard-Andersens «Acid-base chart» to calculate BE. We simulated 400 different acid-base statuses and used the algorithms worked out by the producers of the 4 mentioned instruments. We found out that there were differences between the four instruments, in particular for base excess with high positive values (Metabolic alkalosis). This could have clinical consequences. My proposal was: We have to standardize the calculations. This was done, and I could give an answer 10 years later that the instruments calculated equally. I was much involved with The Great Transatlantic Acid-Base Debate that started in 1965. Professor John W.Severinghaus tried to reconcile the parties in the 1980`s with the article «A Boston- Copenhagen Detente». This was turned down by the Boston group! In my presentation, I will talk about an important meeting in the year 2000 in Elsinore north of Copenhagen. There were 35 delegates from the USA. The Trans-Atlantic discussion continued here. In my presentation, I will tell you about other interesting things from this meeting!

FRIDAY

Dynamics of the functional respiratory system parameters under the influence of mountain meteofactors. Research at the Elbrus medical-biological station

N.I. Aralova, P.V. Beloshitsky

The well-known Ukrainian pathophysiologist, mathematician, climber P. V. Beloshitsky conducted scientific research in the field of aerospace, mountain, extreme medicine, bioinformatics, mathematical and adaptive biology, sports medicine. In 1961 he graduated from the medical faculty of the Kyiv Medical Institute. He studied the state of organisms in extreme conditions, the practice took place in the Caucasus under the guidance of Acad. USSR Academy of Medical Sciences M. M. Sirotinin, becoming his student, a representative of his scientific school. In 1964, Pavel became the first Ph.D. "Space Physiology". Participant in the simulation of landing on the moon in the eastern crater of the Elbrus summit under the USSR Space Programs (1966–1968), in the cosmonaut training units. Under his leadership and direct participation in 1966-1968, a laboratory was installed in the crater of the highest peak in Europe (Elbrus), and work was carried out to simulate life conditions on the Moon and the first helicopter landing in the earth was made at an altitude of 5621 m.

He was the first, who studied the combined effect of cooling and overheating under conditions of hypoxia. The work was carried out first under expeditionary conditions, since 1973 in stationary ones: laboratories with the best equipment at that time were built on EMBS. The second higher education is the Faculty of Mechanics and Mathematics of the Kyiv State University. Shevchenko (1972). In 1983 he defended his doctoral dissertation. Worked at the Institute of Physiology. Bogomolets of the National Academy of Sciences of the Ukrainian SSR (Kyiv). In 1972-1993 was the director of the Elbrus Medical Biological Station (EMBS) of the National Academy of Sciences of Ukraine (Terskol, Caucasus, height 2100 m); In those years, the station became the world's leading center for studying the problems of hypoxia, adaptation, space biology and medicine, training cosmonauts, climbers, special contingents, etc. After the Chernobyl tragedy, EMBS launched large-scale studies of the effect of radiation on the body, the development of methods of treatment, and rehabilitation of the irradiated. Becoming the founder of the program "The Banner of Ukraine on the Peaks of the World", he went to the outstanding peaks: Mont Blanc, Elbrus (1990), Kilimanjaro (1995), Huayna Potosi (1994), Aconcagua (1997).

Currently, the ever-increasing intensity of human activity in unfavorable environments, and the need to perform work in various extreme disturbances, significantly increase physical, mental, and emotional stress on the human body, leading to pronounced changes in functional systems. Therefore, studying the human body’s adaptation to working in extreme environments is urgent. The work of climbers is an adequate model for studying the combined effects of hypobaric and exercise hypoxia. The need to process large amounts of information requires the use of modern computer technology that allows the training process in the training of climbers, which would repeatedly, almost in real-time, speed up the processing of survey data and accumulate for further use in determining the current status and forecasting regulatory reactions of the body to external and internal disturbances.

We have developed an automated information system of functional diagnostics using the model of regulation of oxygen regimes of the body and its practical application in the study of highly qualified climbers. Based on the model of regulation of oxygen regimes of the organism, the automated information system for functional diagnostics of persons in conditions of extreme disturbances is

constructed. The results of approbating the offered software for research on a group of highly skilled climbers are presented.

The proposed software allows the use of a model of oxygen regimes of the body in real-time, i.e., repeatedly accelerates the processing of data obtained during the survey of athletes, allows centralized collection of information for its pre-processing, storage, and collective use, allows you to compare the basic parameters characterizing the functional respiratory system during natural sports activities and obtained during ergometric loading.

FRIDAY

Human adaptation to high mountain conditions at the altitude of 2800 m above sea level

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The main purpose of the study was to study the adaptive mechanisms of residents living in the Tien Shan mountains at an altitude of 2800 m above sea level. The results of our research allow us to judge what is the physiological norm and what is the adaptive norm of a person living in high mountains, and how to distinguish the adaptive state from the functional and pathological changes that occur in the body of mountaineers. The adaptive norm is the limits of system change under the influence of the current environmental conditions, under which structural and functional connections with the environment are not violated, ensuring the continued existence of the system. Since the adaptive norm is not always fully realized, there is an individual adaptive norm. Ensuring normal functioning is an indicator of the adaptability of the system, and the characteristics of the structure are the norm of adaptation (Dzhunusova G.S., 2013).

Today there is a need to systematize the acquired knowledge. For example, with regards to the approach to assessing the adaptive state. What we consider adaptation is when the human body begins to function optimally at a new proposed level with the development of a new matrix of interconnections at the central level and an adequate relationship between the main systems of the human body. How long will the adaptive state last, what does it depend on? There are many questions and more than answers. Therefore, monitoring and population studies are relevant to assess the health status of the population, to identify risk groups and prevent prenosological conditions, etc. The human body is a dynamic system with self-regulating primary and secondary subsystems that allow you to adapt to constantly changing environmental factors and maintain its functional optimum. (Sirotinin N.N., 1963; Soroko S.I. et al., 2003; Dzhunusova G.S., 2013; Novikov V.S., Soroko S.I., 2017, etc.)

Among the indigenous inhabitants of the highlands, living at an altitude of 2800 m above sea level there is a reduced content of ACTH with an increased level of cortisol, indicating the functional stress of the body and the continuing adaptation of the highlanders. The pituitary-adrenal system exerts a temporary regulatory inhibition of hormone synthesis, reflecting the functional transition of the body's acute reactions into persistent adaptive shifts. Activation of the sympathetic-adrenal system with a decrease in the hormonal response against the background of the activity of neurotransmitters. Unidirectional shifts (increasing) in the levels of norepinephrine and corticosteroids characterize the specific functional relationships between them, which serve as effective methods for assessing the

adaptive states of the body of highlanders. The functional tension of the pituitary-thyroid system, manifested by a relatively elevated or normal level of thyroid hormones with a reduced level of TSH in some mountaineers, indicates adaptive changes in the body of mountaineers.

The discrepancy between the adaptive capabilities of the highlanders' organism and the changed environmental conditions can cause disadaptive shifts, stress and fatigue of the central nervous system. Disadaptation states in highlanders occur against the background of hypoxic hypoxia, where the leading mechanism is the deficit of functional reserves of the main body systems, as well as energy imbalance, which affects the severity of psychoemotional reactions, etc. criteria that make it possible to judge the functional state of the central nervous system, the methods and degree of compensation for brain disorders. It has been established that high stability, plasticity of the central nervous system and psychophysiological reactions are the main physiological resources for effective behavior in the mountains, which ensure optimal adaptation of mountaineers and make it possible to identify groups of individuals with an unstable functional state subject to environmental stress.