Abstracts

7th CHRONIC HYPOXIA SYMPOSIUM

Feb 23 - Mar 2, 2019 La Paz – Bolivia

Dedicated to the Late Danish Physiologist Prof. Poul-Erik Paulev

The 120-th anniversary of academician N.N. Sirotinin

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The generator of scientific ideas N.N.Sirotinin along with his research school, have been a great contribution to the different spheres of physiology – mountain, extreme, ecological, evolutionary, comparative, aerospace, age physiology; in radiation and sports medicine; in allergology, immunology, hypothermia, reanimatology. His achievements were outlined in: P.V.Beloshitsky "Annals of biomedical research at Elbrus region (1929 - 2006)".

Investigations of the hypoxic states was especially important for N.N.Sirotinin. He started his hypoxia investigations in 1929, first in expeditionary conditions, then – at stationary Elbrus Medical–Biological Station (EMBS, established on 1972; Professor P.V.Beloshitsky was EMBS Director from 1972 to 2006). EMBS included buildings for space physiology laboratory, clinical department, unique thermobarocamera, temporary laboratories at different mountain altitudes up to 5621m. EMBS was an International Center for studying mechanisms of hypoxic states development – not only their destructive mechanisms, but also constructive ones with the purpose of improving the health, the organism resistance to extreme factors and different diseases' treatments. Sirotinin had published a book "Life on Heights and Disease of Heights" (1939, in Ukrainian), it had no analogues in the world at that time.

The studies of hypoxic states and their mathematical modelling carried out by N.N.Sirotinin scientific school became the basis for new methods of hypoxytherapy for the first time in world practice; they contributed to transformation of hypoxia from descriptive-experimental science into an exact one. Thanks to these studies of hypoxic states and their mathematical modeling, concepts were developed in regards to "optimal stepwise adaptation to conditions of mountain heights", "changes in reactivity and resistance in phylogenesis and ontogenesis"; "Elbrus". Likewise, classification of the hypoxic states was proposed and genesis of hypoxia during irradiation and hypothermia were invented. Peculiarities of pharmacological substances' influence in hypoxia were determined and as a result of this the necessity of a new science – space (ecological) pharmacology was substantiated on 1964.

Today, due to the number of objective reasons, investigations of hypoxia in my Ukraine have lost their leading positions. Therefore I – Professor P.V.Beloshitsky, direct successor of Sirotinin's investigations, would like to pass the "Crown" of "Capital of Hypoxia" from Kyiv, Ukraine to La Paz, Bolivia to the High Altitude Pulmonary and Pathology Institute of Professors Zubieta (father and son) and now Dr. Natalia Zubieta (grandaughter) who also follow the same scientific traditions.

Chronic hypoxia and biospaceforming: adaptation and survival beyond earth

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Humans cannot expect to go to high altitude cities and continue to be sea level residents. Adaptation is a fundamental process in order to secure survival of the species. And it implies change, but with adequate functionality. The same concept applies to space travel. One of the transcendental mechanisms of adaptation to high altitude is the increase of red blood cells. This is the biological response to chronic hypoxia that allows for a most efficient and less energy consuming mechanism of oxygen transport to the tissues. And it should never be considered a negative effect, even within disease. One of the key issues is that Chronic Hypoxia becomes a fundamental tool. It gives humans and other species an advantage of survival, on earth and even beyond earth. There are time frames for an adequate and suitable adaptation. This is explained with the Adaptation to High Altitude Formula. Additionally and actually paradoxically, there is more tolerance to hypoxia, the higher one goes in altitude. On the summit of Mt. Everest at 8842m, humans are 6-fold more tolerant to hypoxia than at sea level. These fundamental observations show us that as we go high in a mountain, we are actually reducing the barometric pressure and we are getting closer to space, where the pressure is 0. And our adaptation is perfect, being the cities of La Paz and El Alto, examples with 2 million people carrying out normal lives. Exposure to acute hypoxia is altitude and time related. The faster one goes, and the higher one goes, the possibility of suffering Acute Mountain Sickness is greater. However, if enough time is given, to carry out a smooth adaptation, and the subject remains at a fixed altitude, the biological systems adapt, in a most efficient way to chronic hypoxia. Even at the summit of Mt. Everest.

Hence why try to remain with the optimal body for earth habitation? Why use so much oxygen pressure? Why expect to live surrounded by an atmosphere with a barometric pressure similar to that of sea level in planet earth? Why expect the future habitable planets to be like earth?

Humans have to understand that it is not only the planets that have to be terraformed, like Mars. It is us and all living beings that have to change and adapt to other worlds i.e. BioSpaceforming, and continue life and intelligence in totally different conditions.

Bio = life, Space = Universe, Forming = Adaptation

BioSpaceForming is the adaptation of all living beings on earth to outer space. Humankind with the highest intelligence, evolving into the future beyond earth.

It is our brains that have to travel, not so much our limbs. Those were designed for planet Earth, for gravitational pull. But Earth is just a station, possibly that we inhabited temporarily, and now the future lies ahead. It is the neurons that have to evolve. They have to learn to live with less oxygen, like we do at high altitude. High altitude residents are more prepared for space habitation. They have already taken the first big step: greater tolerance to hypoxia.

Molecular mechanism underlying the cardioprotective effects conferred by adaptation to chronic continuous and intermittent hypoxia

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Adaptation to continuous hypoxia (CH) confers protection against lethal myocardial injury caused by acute ischemia/reperfusion (I/R) insult. The salutary effects can be demonstrated both in the open-chest model of myocardial infarction and in freshly isolated ventricular myocytes subjected to simulated I/R. However, a single daily interruption of the hypoxic exposure with a brief normoxic episode can abrogate the CH-induced cardioprotection. Regarding chronic intermittent hypoxia (IH), the duration and frequency of daily hypoxic and normoxic episodes are critical determinants of cardiac ischemic tolerance. While chronic IH consisting of repeated cycles of hypoxia/normoxia lasting several minutes each (hypoxic conditioning) or a single daily hypoxic episode lasting several hours is cardioprotective, chronic exposure to fast (seconds) cycles of severe hypoxia/normoxia simulating obstructive sleep apnea syndrome aggravates heart injury caused by I/R. Although many factors have been shown to play a role in the ischemia-tolerant phenotype of hearts adapted to protective modes of CH or IH, the detailed underlying mechanism remains incompletely understood. We have shown that the induction of cardiac ischemic tolerance requires signaling via moderate levels of reactive oxygen species (ROS) and pro-inflammatory cytokines such as TNF-a during adaptation period resulting in increased capacity of myocardial antioxidant systems and activation of cytoprotective pathways involving mitochondrial ATP-sensitive as well as large-conductance calcium-activated potassium channels. These adaptive responses are absent in the non-protective mode of CH associated with brief daily reoxygenation, which leads to excess formation of ROS and oxidative stress during I/R insult.

Unilateral common carotid artery occlusion and brain histopathology in rats pre-conditioned with sub chronic hypoxia

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Background: The importance of cerebral ischemia in clinical practice has stimulated the development of experimental models of its various forms; global, regional, complete and incomplete, permanent and transient. *Objectives*: The study was aimed to assess unilateral common carotid artery occlusion and its impact on brain pathophysiology in sub chronic hypoxia pre-conditioned rats. *Methods:* Rats (200±20 g) were randomized in to three groups. Group 1 served as sham, group 2 were normoxic (21% O2, 79% N2) and group 3 were pre-conditioned with hypoxia (10% O2 and 90% N2) for 21 days prior to left common carotid artery occlusion (LCCAO). ECG and pneumogram were continuously recorded by using Biopac 4.1. The LCCAO was done for 75 minutes followed by reperfusion under anaesthesia. Serum MDA and NO levels were estimated in all the groups of rats before and after the cerebral ischemic experiments. Neurological scores were recorded. Brain histopathology was carried out after sacrificing all the rats after 12 h experiment. There were no changes in HR,RR and BP during entire experimental protocols until sacrifice at the end of 12h. Remarkable neurological deficits were found in both group 2 (normoxic) and group 3 (hypoxic) rats but higher neurological deficits were observed in group 2 rats. Serum MDA and NO levels in group 2 (normoxic) rats following 12h of reperfusion showed a remarkable increase compared to pre occlusion levels which showed remarkable decrease in hypoxia pre-conditioned rats. On histopathology of left (ischemia induced) and right cerebral hemispheres of group 1 (sham) did not show any specific histopathological changes. In case of group 2 (normoxic) rats, right cerebral hemisphere (non occlusive) showed no areas of ischemia induced brain changes but in left side (left common carotid artery occluded side) there were features of ischaemic brain damage involving mainly frontal, frontoparietal regions of the cortex and basal ganglia (striatum) particularly in the lateral segment of the caudate nucleus were observed. In case of group 3 (hypoxia pre- conditioned) rats, there were less ischaemic damages, compared to left side of the normoxic rats were found. *Conclusion:* This study demonstrates that hypoxia preconditioning can reduce brain injury after focal ischemia.

Hypoxia and the reconfiguration of neuronal networks.

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All mammals developed effective strategies to cope with reduced oxygen availability or other metabolic, environmental and behavioral challenges. An important prerequisite for survival is the necessity to maintain functional integrity during times of extreme challenges. This is not only important for the neuronal control of breathing and the cardiovascular system, but also for all other cortical and subcortical networks in general. Mammals adapt to hypoxia through a highly coordinated, systems- and cellular level reconfiguration involving the partial shutdown of some but not all organs. This reconfiguration is controlled through a similarly complex reconfiguration at the cellular and network level within the central nervous system. The neuronal network controlling breathing is well suited to unravel the underlying mechanisms. This network is not only functionally well defined, but it is also amenable to a rigorous cellular and subcellular analysis. Using modern transgenic, optogenetic and molecular techniques we identify the critical microcircuits for breathing and demonstrate that hypoxia and reactive oxygen species significantly alter the composition and even distribution of respiratory activity within the ventral respiratory column. This network reconfiguration involves the differential activation and inhibition of identified excitatory and inhibitory respiratory neurons as well as glia. The reconfiguration is adaptive in the presence of chronic hypoxia, but it becomes maladaptive following exposure to severe chronic intermittent hypoxia leading to disordered breathing and disturbed cardiorespiratory coupling.

Impact of erythropoietin in the neural control of hypoxic ventilation

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Erythropoietin (Epo), the main regulator of red blood cell production, has several functions in addition to classical erythropoiesis. Epo, its receptor (EpoR) and its endogenous antagonist (soluble EpoR) are present in a broad range of tissues, including the brain. Several elegant research performed during the last decade reveled that Epo has a complete new role: Epo exerts a protective function upon hypoxic and ischemic injury. Our studies have also contributed to this new concept of Epo. We demonstrated that Epo prevents the respiratory depression by activating the brainstem respiratory neurons and the carotid body glomus cells. By using transgenic mouse lines overexpressing Epo in brain only (Tg21), and in brain and plasma (Tg6), we demonstrated that cerebral Epo enhances the ventilatory response to acute and chronic hypoxia by interacting with brainstem respiratory centers. Furthermore, as changes in arterial Po_2 and Pco_2 are as well sensed by peripheral chemoreceptors to adjust lung ventilation to the metabolic demand, in a recent study we tested the hypothesis that Epo have an impact in the modulation of carotid body (CB) chemoreceptors in response to hypoxia and hypercapnia. To this aim, we used isolated and perfused *ex vivo* CB preparations from adult male Sprague Dawley rats. Our results strongly suggest that the plasma Epo concentration determines the CB chemo-response to hypoxic and hypercapnic conditions. All together, these novel findings are relevant to better understand respiratory disorders, including those occurring at high altitude.

Acid imbalance bordering base in a public hospital of Mexico City at 2238m. Case report

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History of present illness:
Female patient (Weight 58 Kg, height: 1.50 m.), Has a history of marked decay, sensory alterations in time, space and person, polypnea, decreased visual acuity. Without pulmonary rales, with abdominal pain in left hemiabdomen, abundant diarrhea without blood or mucus, frequent vomiting, with abdominal peristalsis, with anuria, without fever. At admission at emergencies he presented CF: 120 per min, AT: 90/60 mmHg, RF: 27 / min, Temp 36.6 °C. With a history of Diabetes Mellitus of 11 years, hypothyroidism without taking levothyroxine for 1 month, hypertension from 1 year, treated with losartan 50 mg / 24 h. The patient was taking the following medications: metformin 850 mg / 8 hours, glibenclamide 5 mg / 12 hours, linagliptin 5 mg / 24, Pioglitazone, lozartan 50mg / 12 h.

Discussion:
The patient entered the hospital with severe decompensation that endangered her life, despite the metabolic variables she was conscious but with important neurological deterioration, without data of structural coma or focalization. With extreme metabolic acidosis that according to NEJM (1), would not be compatible with life by pHa, HCO3 and paCO2. These last two gasometric variables correspond to an extreme compatible with a sample taken at 8,800 meters above sea level.

Treatment:
Sustained treatment with mechanical ventilation, vasopressors, sodium bicarbonate, fluid intake in the emergency department and initial stage in intensive care did not improve the patient's evolution, even prolonged acidosis, until 13 hours from November 30th. The renal support did not favor the development of hemodynamic instability, therefore it has a main indication in these cases. Finally, the replacement of hormones hydrocortisone, insulin and levothyroxine contributed to stabilize the depressed metabolism.

Conclusion
Acidosis not compatible with life reverted with the treatment used. Objectively for this case the therapeutic gasometric parameters according to altitude above sea level, for sea level, Mexico City, La Paz el Alto and Bajo with respect to bicarbonate can be standardized based on clinical response, improvement in systemic perfusion, regardless of the value.

Poly-erythrocyt-hemia, a sign of multiple pathologies confused as chronic mountain sickness where there is NO loss of adaptation: A presentation beyond life.

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Some high altitude residents can present higher hematocrits and hemoglobin than normal residents. This was originally described as Chronic Mountain Sickness (CMS) and was mistakenly referred to as a "loss of Adaptation". In my criteria, during my life with over 63 years medical of practice at 3600m of altitude in the city of La Paz, where thousands of patients were observed, it became evident over time, that there were great mistakes in the interpretation.

First, Most scientists use the term "Chronic Mountain Sickness" implying "one disease" at high altitude, where, in reality, it represents multiple pathological entities located in the different organs, with lung and heart disease predominance, but also in kidney, carotid body, central nervous system, in the gonads, and very rarely in the bone marrow and the blood.

Second, the wrong use of the terminology referred to as polycythemia, increased polycythemia, erythrocytosis and excessive erythrocytosis. These terms are not accurate in medical epistemology, where for something to be considered as knowledge, it must be true in nature. I created the precise term: PolyErythrocytHemia (PEH) where: Poly=many, Erythrocyt=Red Blood Cells and Hemia=in blood. This is precisely what the sign of increased red blood cells is, in all these pathological entities at high altitude.

Third, it is always associated to hypoxemia. As far as current knowledge goes, hypoxemia can be due to: hypoventilation, pulmonary shunts, diffusion alterations and uneven ventilation/perfusion. And this is where all investigation and diagnosis should lead, in these pathologies at high altitude.

Fourth, therapy should never be focused on the unphysiological idea of reducing the number of red blood cells to a "normal level". This wrong and primitive concept has led to erroneous strategies such as bleeding, destroying red blood cells with toxic and prohibited drugs such as Phenylhydrazine and even radioactive substances, that only led to death due to complications in the endothelium and multiple organ failure, including liver and kidneys. Additionally, I opposed the wrong idea of reducing the ingestion of red meats, and even red vegetables, assuming that the organism should not have the nutrients that red blood cells require, as though it were only a hematological disease, comparable to a blood cancer.

Fifth, When concurrent pathologies are found associated to CMS, it cannot be concluded that hypoxia produced the pathologies, quite the contrary, it is the pathologies that produced what was known as CMS.

Finally, the term "Loss of Adaptation" seemed totally illogical and we stood within the International Consensus Group on the Definition of Diseases at High Altitude with a dissenting point of view, thereby disagreeing with the wrong use of this term. Living organisms never loose adaptation. This is an antithesis of life: Adaptation of deficient organic function due to diverse diseases must maintain cellular function, in the hypoxic environment at high altitude through PolyErythrocytHemia. I wrote, during my life, on July 22, 2010 "FOREVER: LOSS OF ADAPTATION" DOES NOT EXIST!", which is easily accessed through the web. "CMS or rather PolyErythrocytHemia is found in residents at high altitude with some abnormal pulmonary function (increased shunt, impaired diffusion, uneven ventilation and/or hypoventilation), sequelae of diseases of diverse etiopathogenesis and likewise alterations in others organs. These lead to a sustained (and variable) low oxygen saturation and cyanosis, giving rise to pulmonary hypertension and increased red blood cells, as a compensatory mechanisms of adaptation to the disease under chronic hypoxic conditions. The symptoms and signs are reversible by descent to sea level or by increasing the PIO2." Once again, next to my ashes, in my mausoleum at the IPPA High Altitude Museum, remembering my scientifically productive 90 years of existence, I affirm forever that: *"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 (loss of adaptation) which would inevitably lead to death"*

Cardiovascular function and chronic mountain sickness in the highest city of the world

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While large populations live permanently at high altitude (>2500m) worldwide, the mechanisms underlying their tolerance to chronic hypoxia and responsible for the occurrence of chronic mountain sickness (CMS) remain to be elucidated. Although excessive erythrocytosis (EE) is thought to be the main mechanism responsible for CMS symptoms, the relationship between hypoxemia, hematocrit and CMS remains to be clarified. The present study investigates 1594 individuals living in La Rinconada, the highest city in the world (5100-5300m). Based on individual clinical characteristics, subjects were categorized according to i) the presence of EE, ii) CMS symptom severity and iii) CMS diagnosis (EE+symptoms). The prevalence of EE (44%) and CMS diagnosis (26%) was high compared to other highlander populations. Interestingly, individuals with EE reported few symptoms while symptomatic individuals had lower hematocrit compared to asymptomatic counterparts. Multivariable analysis revealed that older age and being male were associated with EE while younger age, lower number of years spent in La Rinconada and lower hematocrit were associated with CMS symptoms. These results suggest that high hematocrit values might be required to reside in La Rinconada without symptoms while the mechanisms underlying cardiovascular and neurological symptoms reported by many highlanders remain to be elucidated.

Chronic Mountain Sickness among Cerebro-Vascular Accident (CVA) patients in a Hospital at 3650 m in La Paz, Bolivia

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At high altitude, there is a lower barometric pressure and hence lower Partial Inspired Oxygen Tension (PIO2). High altitude residents have higher hematocrit and hemoglobin values, than sea level residents in the Andes. This is a natural adaptation process, being the most energy efficient mechanism of adequate oxygen supply to the tissues in a hypobaric environment.

Some people at high altitude, however, present higher hematocrits and hemoglobins above those of the normal residents. This has been described as Chronic Mountain Sickness. The overall fear is that this higher hematocrit with a high viscosity blood, can give rise to thrombus and a series of multiple obstructive circulatory pathologies, being the most feared, the Cerebro-Vascular Accidents (CVA). These are a most serious events that can bring about diverse types of paralysis, mental disfunction or even death.

In our Institution at 3500m of altitude, we consider a hematocrit higher than 58%, a value above the normal healthy subjects. The incidence of high values of hematocrit and hemoglobin in the city of La Paz, obtained from a hospital laboratory records located at 3550m was 28% for males and 11% in females. According to current beliefs, these patients are at risk of suffering CVAs. We suspected from many years back, based on clinical experience, that CMS patients don't suffer much CVAs.

Records of all patients diagnosed as CVAs were reviewed during a 3 year period, from Jan 2015 to Nov 2017, at the Hospital Arco Iris located at 3650m of altitude in the city of La Paz. Of 96 people found to have been diagnosed as suffering from CVA, only 10 had a concomitant Poly-Erythrocyt-hemia (an increase of the hematocrit and hemoglobin), who would be considered as suffering from Chronic Mountain Sickness.

Upon careful review of the diagnosis of all these 10 patients, it became evident that all of them suffered concomitant diseases well known to be causes of CVS. Among them, 9 patients (90%) suffered likewise Arterial Hypertension. Other pathologies found included Diabetes Mellitus Type 2, cardiac insufficiency, stress and dislipidemia.

It becomes clearly evident that although these 10 patients, had an increased hematocrit, one could not attribute the AVC solely to it, but rather to the most common cause: Arterial Hypertension. An event that happens not only at high altitude but also, recurrently, at sea level.

These findings suggest that a high hematocrit is possibly not the cause of CVAs at high altitude, as there are other pathological entities involved, that seem to be the primordial alteration. The fear of "thick" blood producing CVAs is questionable. More extensive studies, could confirm this observation.

Endothelial dysfunction at high altitude

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Endothelial dysfunction (ED) is an important component in the pathophysiology of atherosclerosis, coronary and cerebrovascular artery disease. Current knowledge indicates that this condition may be reversible and that its progression can be slowed down, hence decreasing atherosclerosis advancement. Healthy endothelium produces nitric oxide (NO) a molecule with relaxing properties, but it also produces endothelin-1 and angiotensin, which have vasoconstrictor properties.

When NO production is decreased and the production of reactive oxygen species (ROS) is increased, vascular tone shifts to vasoconstriction and there is an enhanced expression of cytokines, adhesion molecules and chemokines, in a process known as endothelial activation. When the endothelium is activated, there is a localized inflammatory condition in which leukocyte and platelets adhesion is increased, in the same manner as when there is a systemic infection. Dyslipidemia, hypertension, hyperglycemia, hypoxia can induce endothelial activation and lead to ED.

ED can be measured by determining the serum levels of NO synthetase, endothelin 1, the urinary levels of DNA degradation products or the values of flow mediated dilation (FMD). FMD is a procedure that using Doppler ultrasound can determine the degree of intrinsic and extrinsic vasodilation. At high altitude, healthy Andean subjects have shown higher levels of vasodilation than genetically adapted Tibetans or Sherpas, as well as lowlanders. Their response to sublingual nitrate (a drug that evaluates extrinsic endothelial function) is also superior in the Andeans, without differences in age as is reported at sea level. By contrast, ED is high in Andeans who have developed comorbidities: 100% in diabetics, 68.8.8% in obese individuals and 56.6% in hypertensives. For those who had ED and lived at high altitude, vascular response was worse than lowlanders, with as much as 58.6% having intrinsic and extrinsic ED. Current data suggest that endothelial function is better in phenotypically adapted highlanders as compared with lowlanders and genetically adapted individuals, but when ED is present, it is more severe than usual.

Hypertension at High Altitude

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There is considerable controversy about hypertension at high altitude. Even though some physiological mechanisms lead to an increase in blood pressure levels, other cause decrements in its values. Striking discrepancies are observed between Andeans and Tibetan populations. Tibetans are reported to have an increase of 17 mmHg in systolic and of 9.5 mmHg in diastolic blood pressure per each 1000 meters of elevation above sea level. By contrast, Andeans experience a decrease of 5.9 mmHg in systolic and 4 mmHg in diastolic blood pressure for the same altitude proportions. Tibetans have higher density of peripheral capillaries, greater nitric oxide (NO) production in their pulmonary arteries and better oxygenation than Andeans, but consume excessively high amounts of salt, a great amount of alcohol, low potassium, few fruits and vegetables, besides having, in some cases, a mutation in the angiotensin-converting enzyme (ACE) gene. Lowlanders have an upward surge in blood pressure after acute exposure to high altitude due to an increase in adrenergic tone, endothelin levels and arterial stiffness, but these derangements are controlled when the exposure to hypoxia is chronic.
Tibetan natives, despite their higher tendency to develop hypertension, have lower carotid media thickness, less beta adrenergic receptors, higher flow mediated dilation (FMD) responses than lowlanders and additionally lower carotid pulse pressure.

Could high altitude affect the prostate health?

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Many physiological responses to high altitude (HA) exposure have been studied. Different hormones, including sex hormones are involved in process of high altitude adaptation. Testosterone, the main androgen which participates in male reproduction, also is one of the erythropoiesis regulators.
Epidemiological studies showed that HA exposure are associated with higher prevalence of cancer and increase the risk of death by this disease. However, there is only limited evidence available for the effect of this exposure in prostate health, even though it is well-known that this organ is androgen-dependent. Based on the literature, it is assumed that this effect of androgens on prostate illness at sea level could be worse at HA.
In addition, common factors and biomarkers such HIF-1, SENP1, IL-6, CRP, including testosterone, are related in both high altitude diseases and prostate illness.
In conclusion, better understanding and future research of physiological and pathological prostate illness in HA conditions need be considered.

Neuronal mechanisms underlying central and obstructive sleep apnea

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Apnea, the cessation of breathing, is a physiological and pathophysiological phenomenon common in the pediatric and adult patient community. Indeed, with the increased prevalence of obesity, sleep apnea has become a problem of epidemic proportions. Among the different forms of apnea, obstructive sleep apnea (OSA) is clinically the most prominent manifestation. OSA is characterized by repetitive airway occlusions that are typically associated with peripheral airway obstructions. Yet, even though peripheral airway obstruction may be initial cause of OSA, the manifestation of the disease involves dynamic interactions between chemo- and mechanosensory reflexes, behavioral state, neuromodulation, and the differential activation of the central respiratory network and its motor outputs. An important driver of the disease is the Chronic exposure to Intermittent Hypoxia (CIH). CIH directly affects the central respiratory network which triggers a vicious cycle: CIH- induced desynchronization among the respiratory neurons leads to hypoglossal apneas that in cause further episodes of intermittent hypoxia. CIH itself will affect the cardiorespiratory coupling leading to autonomic consequences, that become major contributors to morbidity and mortality. Not only OSA, but also central apneas (CA) have multiple, and partly overlapping mechanisms. Thus, we conclude that the mechanisms underlying OSA and CA are neither "exclusively peripheral" nor "exclusively central" in origin.

Functional foods for inflammatory disorders such as metabolic syndrome and inflammatory bowel disease

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Functional foods provide health benefits in chronic diseases such as obesity, hypertension, diabetes and inflammatory bowel disease, in addition to nutrition. The metabolic syndrome of central obesity, insulin resistance, elevated blood pressure, impaired glucose tolerance, non-alcoholic fatty liver disease and dyslipidaemia is due to chronic low-grade inflammation, including chronic hypoxia in fat pads. A diet high in fructose and saturated/trans fats induces these cardiovascular, liver and metabolic signs in rats and components of foods can reverse all these symptoms in diet-induced obese, hypertensive and glucose-intolerant rats. In particular, anthocyanins from Gueen Garnet plums and tropical Australian native fruits such as Davidson's plums, polyphenols from Garcinia fruits such as achacha and mangosteen, and algae lowered blood pressure, prevented inflammatory cell infiltration into the heart, liver and fat pads, improved plasma lipid profiles and decreased plasma inflammatory biomarkers. All these interventions could be produced commercially, sustainably and cost-effectively in Australia and South America with the aim of reducing the incidence of metabolic syndrome and inflammatory bowel disease, and decreasing the risk of costly cardiovascular and metabolic disorders, especially in regional areas. Further, the effectiveness of indigenous fruits and vegetables in chronic inflammatory disorders have rarely been defined

What is the critical bad prognosis pco2 level at high altitudes?

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I will present a discussion of population dynamics, its effect on healthcare, analysis of cost and development of cost effective measures of continued care. The concept of prognostication and giving complete information to the patient so that they can make adequate decisions towards end of life. Discuss how in Chronic Obstructive Pulmonary Disease (COPD) patients at sea level, chronic PCO2 levels >50 mmHg carries a bad prognostic index. The question would be at what level of PCO2 is a bad prognosis in high altitudes environments. This is fundamental as at high altitude the PaCO2 is progressively lower. Consequently patients living under chronic hypoxia need to have different PCO2 levels carrying a bad prognosis.

Hormonal profile and bioelectric activity of brain in mountaineers

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The aim of the study was to characterize the relationship of the bioelectrical activity of the brain with the hormonal profile of the inhabitants of the highlands (n = 92 and n = 48, 2800 m). A decrease in the spectral and probabilistic indexes of the alpha rhythm and an increase in the severity of the brain theta rhythm in high-mountain residents, which inevitably arise with prolonged exposure to extreme factors at high altitudes, have been revealed.

Under the influence of the extreme factors of high mountains, the levels of hormonal parameters in healthy mountaineers deviate from the norm, which is typical of lowland inhabitants. Indigenous people of highlands have their own inherent standards of endocrine functions, their inherent conditions of life, their own characteristic for specific conditions of life, the values of hormone levels, which are established under the influence of a complex of climatic and geographical environmental conditions. There was a general tendency to a decrease in the functional activity of the thyroid gland, hypophysial and sex hormones among the inhabitants of high mountains, with an increase in the level of cortisol. The essence of the changes was reduced to the maximum saving of energy consumption for providing the homeostatic and metabolic functions of the body.

The analysis revealed system markers at the level of effector systems — this is the levels of cortisol, thyroid and sex hormones. At the level of central regulatory systems, it is TSH and ACTH and the level mediators are the concentration of monoamines (dopamine, serotonin and norepinephrine) in the blood. When comparing the results of the activity of the neuroendocrine systems of the mountaineers with the functional parameters of the central nervous system, two strategies of adaptive behavior in the mountains are defined: active and passive, each of which is characterized by certain parameters of the hormonal profile and EEG parameters. Thus, mountaineers with an active strategy of adaptive behavior have a reduced level of cortisol, a mobilization of sympathetic influences on the cardiovascular system, a low content of sex hormones whereas, mountaineers with a passive strategy of adaptive behavior have elevated levels of cortisol and TSH, indicating an adverse effect of altitude factors on adaptive responses of mountaineers, as well as an increase in the parasympathetic effect on the cardiovascular system.

Central mechanisms of regulation of human functional state in the mountains

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Physiological studies aimed at uncovering the fundamental mechanisms of human adaptation and development of appropriate and adequate methods for the selection of the most resilient individuals capable of life and carrying out work successfully in the mountains, without compromising their health require special techniques.

The aim of the investigation was to study the mechanisms of sensitivity and human sustainability in the mountains with a view to establishing effective screening methods and prognosis of human adaptive capacity.

Diagnosis of functional disorders in humans, both in normal and extreme conditions, involves individual evaluation parameters of their basic functional systems. The most important is the level of central mechanisms of regulation (CMR) in the brain.

Our research determined what types of brain CMR revealed a significant difference in the distribution of typological groups at high altitude (low limits of alpha rhythm of persons type I brain and high limits for persons type III brain). This indicated physiological narrowing adaptive mechanisms in mountain residents, which explain the reduction of spectral and probability indicators of alpha rhythm and increasing severity of theta rhythm, emerging with long-term effects of factors such as CMR voltage, which cause a noticeable redistribution of typological groups among the inhabitants of the highlands.

It is these individuals, the mechanisms of self-regulation of the brain, drive the restructuring of the EEG pattern. When human adaptation to hypoxic conditions in the mountains occur, there is a difficult restructuring of temporal organization of the EEG pattern. This reflects the flow stage adaptation: nonspecific activation, reaction of the brain to hypoxia, compensatory oxygen providing reactions and voltage regulatory mechanisms. The parameters of EEG during adaptation in the mountains will depend on the type of CMR. Violations of the CNS functional state in the mountains and their severity depends on individual sensitivity and human resilience to hypoxia, as well as, adaptive plasticity of the nervous system. While signs of acute mountain sickness can occur in persons of all basic types of brain, their nature and severity increase from group I to group III.

The adaptive behavior depends on the leading role of the most appropriate adaptation strategies adopted by the type of brain that triggers major regulatory systems of the body. The highlanders with high adaptive reserves depend exclusively on ways of strengthening the monitoring mechanisms and a reduced response to the conditions of life in the mountains. However, the highlanders of low adaptive reserves, search for additional reserves due to the high tension of the regulatory mechanisms and the inclusion of autonomic and behavioral adaptation components.

Erythropoietin and caffeine prevent apneic events in male newborn rats exposed to intermittent hypoxia: apnea of prematurity and sex dimorphism

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Owing to the immaturity of the brain, apnea of prematurity (AoP) occurs in more than 85% of infants born with less than 34 weeks of gestational age. AoP is associated with severe and repeated episodes of arterial oxygen desaturation (intermittent hypoxia – IH), which in turn increases the respiratory instability and the number of apneas. While AoP and IH are frequent in preterm boys and girls, there is no data addressing whether IH leads to sex-specific respiratory consequences, neither if drugs targeting AoP are more effective in males or females. In this work, we used rat pups for investigating whether IH-mediated increase of apneas is sex-specific. Furthermore, we investigated whether caffeine (treatment of choice of AoP, but ineffective in about half of the cases), erythropoietin (Epo - a neuroprotective factor and potent respiratory stimulant at neonatal ages), and both drugs together (caffeine+Epo) prevent the IH-mediated formation of apneas in a sex-dependent manner. Newborn rats exposed to IH during postnatal days (P) 3-10 were used in this work. During this time, animals were daily gavage with a vehicle, Epo, caffeine, and Epo+caffeine (10-12 pups/group). At P10 the frequency of apneas at rest were measured (by plethysmography), as an index of respiratory dysfunction induced by IH plethysmography. Our results showed that IH induces 40% more apneas in male than female rat pups. Moreover, results in males evidenced that caffeine and Epo significantly prevent the increase of apneas induced by IH, and that the administration of both drugs together do not provides a cumulative beneficial effect. Results in females showed that nor caffeine, Epo, neither both drugs together prevent from the IH-mediated augmentation of apneic events. We concluded that IH in newborn rats leads to sex-specific respiratory consequences. Our data suggest also that caffeine and Epo have similar effects to reduce the IH-induced apneas in male but not in female animals.

Pediatric medical practice at 2800m in the United States

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The population living at moderate altitude in the US is small but has tripled in Colorado over the last 30 years. These people are considered acclimatized, not adapted like the populations in Nepal, the Andes, and other mountainous countries where people have lived for hundreds of years. The presenter began treating children at 2800m in 2000 after practicing at sea level for 20 years. Children frequently presented with severe hypoxia and cough but were not ill-appearing and had no recent travel. They are told they have pneumonia or asthma and treated with drugs when most do well with oxygen alone. This entity became known at HARPE: high altitude resident pulmonary edema, as reported in two articles published in 2017 and 2018. Other cases of severe rapidly reversible hypoxia are reported after pulmonary contusions and return to altitude and hip surgery with return to altitude. Physicians treating patients at lower altitude who will be ascending should consider the possiblity of HAPE when they reach their home, and not consider acclimatization protective for everyone.

The presenter also noted that twice as many mountain resident children were below the standard CDC or WHO growth charts for height and weight. An initial analysis of over 10,000 data points showed that these little ones recovered after age 2 and were on the standard charts. Currently more data is being organized into an altitude specific growth chart to save parental and professional anxiety leading to unnecessary testing and accusations of malnutrition.

Colonizing high altitude hypoxic environments: strategies to deal with metabolic needs

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The aptitude of mammals to colonize high-altitude environments is limited by their ability to tolerate decreased oxygen availability. Previous research in our lab showed that rats and mice display divergent physiological and molecular responses after acute exposure to hypoxia. This response is traditionally linked with the regulation of metabolism, in consequence, we aimed to identify the strategies underlying the metabolic response of rats and mice to acute and chronic exposure to hypoxia.
SD rats and FVB mice were exposed to hypoxia (12% O_2) for different periods of time. The metabolic rate (VO_2 and VCO_2) and minute ventilation (VE) were measured by indirect calorimetry and plethysmography. The hematological response was evaluated by the quantification of hematocrit and hemoglobin concentration. As the brain is highly dependent on oxygen, we assessed the mitochondrial respiration in brain cortex using the high-resolution respirometer O2k (Oroboros Inc.).
In comparison to normoxic controls, mice showed a higher metabolic rate after 7 days of hypoxia. No change in rat's metabolism was observed. In line with the increased V_{O2}, mice showed a continuous augmentation in V_E with a peak at 7 days of exposure. Rats showed a weaker rise in the V_E at 6h with no further increase. In brain, mice showed an increased mitochondrial respiration after 24 hours of hypoxia, while those exposed to 7 and 21 days were similar to the controls. Though in rats only weak changes in the ventilation and no response in brain-mitochondrial respiration were observed, they showed a strong hematological response. The hemoglobin concentration and hematocrit increased in a sustained way starting at 24 hours, reaching a plateau at 21 days of exposure to hypoxia. Hematological adjustments occurred in mice only after 21 days.
Our results suggest that mice privilege an increase of their ventilatory activity to cope with hypoxia resulting in an enhanced metabolic rate and preserved mitochondrial activity in brain cortex. In rats, whereas the ventilatory response is weak, they favour a rapid and sustained hematological response. We propose that the process of acclimatization to hypoxia ultimately relies on the strategy of capture, distribution and use of available oxygen for metabolic use.

Erythropoietin: a spaceship shield for traveling evolution?

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Erythropoietin (Epo) is a hypoxia-responsive molecule that acts on erythroid progenitor cells to promote their survival and differentiation to mature erythrocytes. Apart from this canonical role, Epo also promotes adaptive cellular responses to hypoxic environmental challenges and tissue-damaging insults in various non-hematopoietic tissues. In the mammalian brain, Epo and its receptor (EpoR) are expressed by glia and neurons and exert important functions during neural development and in the protective response against diverse types of injuries. Such commitment in the increase of the robustness and tolerance of the nervous system has led to the proposal that, rather than regulation of red blood cell production, Epo's original evolutionary function was providing unspecific and unconditional neural protection. In line, the demonstration that the human recombinant Epo induces neuroprotection and neuroregeneration of brain cells from orthoptera insects (grasshoppers and locust) proved that Epo evolved about 550 million years from an urbilaterian (common to vertebrates and invertebrates) ancestor. However, how Epo is integrated with a highly evolutionary conserved O_2-dependent molecular mechanism is yet unknown. Recent evidence in the literature demonstrates that Epo in the brain (and other tissues) increases mitochondrial energy production, regulates oxidative stress, controls mitochondrial calcium homeostasis, and promotes mitochondrial biogenesis. Because: 1) mitochondria are main O_2 sensitive organelles that play a crucial role in the brain development, maturation, and function, and 2) because these organelles are known for having shaped the fabric of life and its evolution, we propose the hypothesis that the endosymbiosis between mitochondria and eukaryotic cells necessitated "chaperone" molecules to monitor the mitochondrial functions and to correct/repair dysfunctions. Specifically, we propose that Epo's original evolutionary function was to support mitochondrial function during shortage of O_2 availability. The aim of this talk is exploring the scientific bases supporting this hypothesis.

Mathematical models of system mechanisms of organism adaptation to hypoxia

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The process of adaptation to hypoxia and the mechanisms that provide it are necessary prerequisites for a high reliability of an organism functioning in various modes of its vital activity.
For a mathematical analysis of the organism's adaptive capacity to hypoxia of various etiologies we used the model of functional respiratory system (FRS). FRS is a controlled dynamic system; it describes the transport and mass transfer of respiratory gases in respiratory tracts, alveolar space, blood, tissue reservoirs and organs (brain, heart, respiratory and skeletal muscles, etc.) The model is represented by ordinary nonlinear differential equations; in it, the regulation is carried out on the basis of compromise resolution of conflict situations that appear between tissues and organs during their fighting for oxygen in conditions of its deficit. It was assumed that the decision about the choice of characteristics' values for compensating influences is made by the decision centre based on the information about the level of functional activity, degree of oxygen deficiency, excessive accumulation of carbon dioxide in all tissue compartments of the organism. This decision was transmitted to executive organs of self-regulation and it increased their functional activity, ensuring the realization of a basic respiratory function.
Analysis of FRS model demonstrated that short-term perturbations of the system which caused hypoxia development could be compensated by the reaction of self-regulation mechanisms that appeared in organism in an evolutionary way — due to intensification of activity of external respiration system, cardiac muscle and vascular smooth muscles. During the medium-term hypoxia influence on organism (weeks) some functional mechanisms that change organism sensitivity to hypoxia might be formed; they increase the efficiency of tissue mass transfer and stimulate erythropoiesis. During the long-term (months, years) influence of hypoxic states on organism, it could no longer compensate this through functional capabilities only. This caused structural changes - hypertrophy of executive regulatory organs and, first of all, to hypertrophy of the left heart ventricle.
In our model the individualization was foreseen taking into account the weight and growth of individual person; the coefficients of organism sensitivity to hypoxia and carbon dioxide excess were used — and these coefficients decreased during a training process.

Studying of sport medicine problems at the elbrus medical and biological station (embs)

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Professor N.N.Sirotinin suggested the concept of gradual stepwise adaptation to mountain heights' conditions in 1950. Since 1960, we started athletes' training in the mountains; and there we found that simultaneous influences of mountains' conditions on organism and individual dosed exercises, accelerate and improve the adaptation process. Therefore we had proposed to use active rest in mountain conditions as a method for improving the health of working people and a means for effectively improving sport achievements.

Inspection of alpinists: We obtained a unique experience in the selection and training of high altitude climbers at Elbrus Medical and Biological Station (EMBS), examining almost all Himalayan expeditions' members known in the former USSR, Russia and Ukraine. Selection and training of climbers under hypoxibaric conditions were carried out through several stages: 1. clinical examination, 2. special clinical, physiological examination during "ascent" in baro-chamber and stress tests, 3. clinical, physiological examination of adaptation processes to mountain height conditions, 4. use of mathematical models of hypoxic states to estimate the speed and efficiency of oxygen transport. Special attention was paid to mental and physical work capabilities, stability for cold, adaptive states and adaptability.

Thermoregulation and sport: This is the problem of temperature homeostasis maintainance in athletes who fulfill intensive physical work in conditions of hypoxia and cold. We found that hypoxic environments reduced heat generation, changing the physical and chemical structures of thermogenesis. During the team of climbers' preparation we also took into account the fact that high adaptability to cold reduced the organisms' adaptability to hypoxia, therefore, training procedures were recommended to be carried out at sea level.

Problems of sports longevity of sports' veterans: We paid particular attention to development of optimal ways to continue active life in sport, especially with hypoxytherapy methods. The "Regulation on the open championship of Ukraine among veterans of mountaineering" was approved in 1997. We found that mountaineering veterans, who train every year in the mountains, have greater capacity of safety when exposed to hypoxic environment and cold. With age, organism ability for adaptation to hypoxia decreased, however, it is not completely lost - older people can adapt to mountain heights up to 5000 m.

Use of Hydrocortisone in non-refractory shock in critical patients at high altitude

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Severe sepsis and non-refractory septic shock are among the main causes of admission to the ICU and, despite recent improvements in clinical outcomes, mortality rates remain high. The effect of hydrocortisone treatment on patients diagnosed with non-refractory shock, specifically on 30-day mortality from any cause, was investigated, because it is not clear whether hydrocortisone reduces mortality among patients with septic shock. It is important to mention that this study population was characterized by living in high altitude conditions.

A greater number of cases of death was found in that group that received hydrocortisone (7 versus 2). It is important to note that the scientific literature on the efficacy of hydrocortisone in patients with septic shock remains controversial. Although the literature mentions a possible influence of altitude on the metabolism of cortisol (endogenous hydrocortisone), no studies have been found that evaluate the effect of high altitude on the efficacy of the exogenous administration of hydrocortisone, much less in the context of non-refractory septic shock

In this regard, it can be inferred that more extensive and well-designed randomized clinical trials are needed to support or deny the use of hydrocortisone in patients with non-refractory septic shock. It is necessary to admit that the findings of the present investigation are insufficient to confirm or deny the benefits of the use of hydrocortisone for the reduction of mortality and the duration of hospital stay in patients admitted for non-refractory septic shock at high altitude.

Factors asociated to polycythemia in miners at high altitude

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Objective: To identify the factors associated with polycythemia in high altitude mining workers. Methods: It was an observational, descriptive, retrospective and transversal study. The sample consisted of 37 workers from the Castrovirreyna S.A. mining company at 3950m which were diagnosed with polycythemia.
Results: It was observed that 54.1% of the workers were employees of Castrovirreyna Cia while the other 45.9% were workers of other contracting companies. The company's workers are mostly between 51 and 60 years old (60%), while in the contracted companies the predominant age in the workers was from 51 to 60 years (71.4%), the highest percentage of workers of both the company and the contracted companies have an experience in altitude, between 11 to 20 years with a residence frequency of 70% and 85.7%, respectively. On the other hand, it could be seen that all workers of the company receive treatment, however, this reality differs in contract workers where only 42.9% received treatment. Conclusion: Age and time of experience can be considered as factors associated with polycythemia.

Moon face due to sudden exposure to high altitude : possible causes and the solutions

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Many of us tell that “Each subsequent day of the same trip gaining altitude in a short period of time, my face gets puffier and puffier. By day four, my face is so puffy, my eyelids are all gross and I'm certain strangers can tell something is wrong with me” what is this phenomenon? Is it an endocrine disorder? Is it seen in all who go to high altitude with sudden gain in altitude? And many more questions still remain.

The only predictor of acute mountain sickness (AMS) is having had it previously, but anyone can get it at any time. The definition in addition to moon face headache after recent ascent plus at least one of the following due to altitude causes water retention, hard time sleeping apart from, (i) tummy troubles (loss of appetite, nausea, vomiting, (ii) tired (fatigue/weakness), (iii) tipsy (dizzy/lightheaded) and (iv) the terrible insomnia (not just frequent waking). These are the four T's. Not sure how to counteract, except to keep sodium levels down, drinking water, maybe some diuretics. This may not be "serious", but it clearly troubles all of us and detracts from our generally feelings of wellbeing.

The moon face syndrome mimicking Cushing is associated with salt retention apart from short term adjustments to new hypoxic environment by altering endocrine system. The drug of choice the Acetazolamide (Diamox), is often prescribed for high altitude problems for excreting sodium and sparing potassium.

Since it is actually a diuretic it might be just the ticket, if not contraindicated for you for any reason. Altitude sickness is caused by hypoxia, which up regulates prostaglandins, that leads to sympathetic stimulation and pain. Probably aspirin blocks this. There have been a few small placebo-controlled studies that show that it works, but that's about it. I say if it works, why not? Except on one trip I took so much aspirin I got nosebleeds. The possible hypothesis and preventive measures will be presented during the talk.