Problems of high-altitude medicine in Kyrgyz Republic: In memory of Professor Mirsaid M. Mirrakhimov

Kırgız Cumhuriyetinde yüksek irtifa tıbbın problemleri: Profesör Mirsaid Mirrakhimov'un Anısına

On October 2, 2008, Mirsaid M. Mirrakhimov, Professor, Doctor of Science in Medicine, Honored Physician of Kyrgyz Republic, Honored Scientist of Kyrgyz Republic, full member of National Academy of Science of Kyrgyz Republic, Emeritus Director of National Center of Cardiology and Therapy of the Ministry of Health of Kyrgyz Republic passed away on the 82nd year of life after severe illness.

Mirsaid Mirrkahimov was born on 27th March 1927 in Bishkek, Kyrgyz Republic in the family of musician. After graduation of Kyrgyz State Medical University in 1948 and fellowship in 1952, he started his professional career as an assistant to professor at the department of internal medicine of Kyrgyz State Medical University and further after defense of dissertation he was elected as the chief of the same department.

Between 1963 and 1978 he served as the Vice-Rector of the Kyrgyz State Medical University.

In 1966 he earned the scientific degree of Doctor of Science in Medicine, scientific title of Professor, 1974-full member of National Academy of Science of Kyrgyz Republic, 1988 -full member of Russian Academy of Medical Sciences.

Since 1977 till 2007 he had served as the director of the National Center of Cardiology and Therapy.

Mirsaid Mirrakhimov, recognized in the world as the scientist, clinician, clinical physiologist, educator, coordinator of science and public health, public benefactor, founder of high-altitude medicine and cardiology, founder of the national school in this field; made a major contribution in the development of biological and physiological basis for adaptation of human to high altitude environment.

Academician Mirrakhimov was the initiator of creation and development of Cardiology service in republic. Scientific Research Institute of cardiology, under his guidance has become a powerful education-scientific-practical complex.

He made a significant contribution by training more than 100 Doctors of Science and PhD title's holders. He published more than 700 scientific works, including 32 monographs, 500 scientific papers, and 19 inventions.

He was the first president of the Association of Cardiologists of Central Asia, president of the Association of Cardiologists of Turkic World, president of Association of specialized medical societies of Kyrgyzstan, member of executive boards of several international medical societies; member of editorial boards of 10 international journals in medicine, including international ones, editor-in-chief of the Central Asian Medical journal. He was elected as deputy of the Bishkek city council and Supreme Council of Kyrgyz Republic.

The work of Mirsaid Mirrakhimov was recognized by government and scientific community by many medals and awards. Considering outstanding contributions of academician Mirrakhimov in the development of national cardiology and internal medicine, training of whole constellation of physicians and scientists and high-qualified specialists, and his active public work, the National Center of Cardiology and Therapy of the Ministry of Health of Kyrgyz Republic was named after academician Mirrakhimov in 2002.

Professor Mirrakhimov will always live in our memory as an internationally recognized scientist, outstanding clinician, who saved and gave as a present the joy of life to thousand of citizens, devoted his whole life for development and well-being of Kyrgyz medical science and practice and strengthening of the health of people of Kyrgyzstan.

(Signed by the government of Kyrgyz Republic and academicians)

Address for Correspondence/Yazışma Adresi: Prof. Dr. Aynagul S. Djumagulova, Director National Center of Cardiology and Therapy Bishkek, Kyrgyzstan
E-mail: nccim@elcat.kg

Kyrgyzstan is a mountainous country and about 2/3 of it is covered by mountains, where the main population of the country lives. About 94.2% of its territory is situated 1000 meters above the sea level and about 40.8% - above 3000 meters.

Today, despite economic difficulties in the country, there are ongoing developments in agriculture and industry in high-altitudes including; mining industry, tourism, alpinism and construction of hydroelectric power stations. Significant amount of people continue to live and work at different altitudes. Large groups of people, including tourists, alpinists and those who carry out professional duties, migrate to the high altitude regions every year.

Conquest of high altitudes, development of agriculture and industry at high altitudes, mining works, military duties and many other types of activity are impossible to accomplish without development of preventive measures directed toward human safety in the unfavorable environment of hypoxia and improving endurance of organism to hypoxia. That is why, investigation of the effects of high altitudes on humans, determination of general rules of adaptation to these special conditions, establishment of methods to increase physical capacity in conditions of high-altitudes and medical selection of people for work at high-altitudes are the important problems of medical science and gain great importance for highlanders, and for people who resides there temporarily as well.

Mountain climate affects human body through many natural factors: low atmosphere pressure and low oxygen partial pressure, high radiation, sharp changes in temperature and humidity. Among them, low atmosphere pressure and low oxygen partial pressure have the leading role. Many biochemical and physiological shifts, including structural changes, provide adaptation to low oxygen pressure in breathing air and low temperature. Circulation and pulmonary systems are the first to respond to hypoxia exposition with the simultaneous adaptive changes in the blood and tissue aerobic capacity. High altitude adaptation causes the series of specific forms of high-altitude pathology, even life threatening. Early diagnostics, development of the methods of adequate correction, as well as definition of clinical manifestations, treatment and prevention of usual diseases among highlanders maintain actuality.

Systematic and in-depth investigations devoted to the problems of high-altitude physiology and pathology, important for healthcare problems solutions and effects of high altitude climate of Tyan-Shan and Pamir have been conducted since 1930s in Kyrgyz Republic.

Since 1962, the scientific research was continued under guidance of professor Mirsaid Mirrakhimov. He for the first time participated in the high-altitude expedition in Naryn town when he was a student. At that time, the problem of adaptation to high-altitudes had not been developed well and the importance and perspectives of physiological studies in high-altitudes were emphasized. Further work at the department of internal medicine of Kyrgyz State Medical Institute (KSMI) and collaboration with well-known physiologists of that time defined the scientific interest of Mirsaid Mirrakhimov in high-altitude physiology. As the chief of the KSMI clinical departments (since 1956-department of internal medicine and since 1966-department of faculty therapy), despite his relatively young age, Mirsaid Mirrakhimov had gained sufficiently high respect, becoming talented team leader who united young colleagues, gave start for scientific studies, increased discipline and improved the level of treatment and preventive work, and educational activity of the departments.

The important step in the development and strengthening of physiological and medical studies at high altitudes was creation by Mirsaid Mirrakhimov of the scientific-research laboratory (SRL) "Physiology and pathology of humans in high-altitude conditions" in 1967. Many of his colleagues worked together at that laboratory: Djailobaev AD, Grinstein BA, Schmidt GF, Almerekova AA, Kochenkova EG, Kudaiberdiev ZM, Dubinina JS, Narbekov ON, Rudenko RI, Hamzamulin RO, Moldotashev IK, Kalko TF, Raimjanov AR, Kitaev MI, and others. There were two departments in the laboratory at the beginning: cardiopulmonary and hematological. Further, in 1971 the department of immunology was created.

At the beginning of the 70s of the past century, the international biological program was formed. One of its chapters was devoted to the problems of human biology, permanently residing in different extreme climate and geographical conditions. Investigations of biological and physiological features of the people living in extreme natural environment (North pole, mountains and deserts), places which had not been yet affected by urbanization and different negative ecological factors allowed assessment of the of human biology. Eighty countries all over the world participated in international biological program and professor Mirrakhimov was selected as the chief of the program on problems of human in high-altitude environment. He further published the series of scientific works on high-altitude physiology and biology of humans, including the chapter in the special volume "The Biology of high-altitude people" (International Biological Program 14) with professor Baker RT as editor, published by Cambridge University Press in 1978.

Mirrakhimov and his colleagues established that physical capacity of humans is in close relationship with the duration of exposure to high-altitudes and altitude per se. The most optimal altitude for maintenance of physical capacity is 200-2500 meters above the sea level. The scientists defined physiological normal values of gas exchange, ventilation and circulation for residents of different altitudes in Tyan-Shan and Pamir, indications and contraindications for treatments by high-altitude adaptation.

The results of complex investigations collected during many years allowed to define 3 phases high-altitude adaptation at altitudes higher than 2500-3000 meters above the sea level: primary, transient and stable (condition of adaptadness). Initially, when individuals are exposed to inadequate hypoxia environment, physiological adaptive reactions develop in emergency order, with the excessive degree of adaptive functional changes required for given conditions. This is justifiable from the point of view of time needed for satisfactory integrated functional changes during long-term adaptation, requiring sometime weeks or months. Gradually, human body adapts to the new environment with further return to usual, basal level of functional parameters. Thus, the hypothesis that individual adaptation should be evaluated upon stabilization of functional parameters at rest, and mainly stabilization of responses to additional stimuli was formed. That is why; the needs to acknowledge the transient and stability phases of adaptation were defined. When the responses to adequate additional stimuli are stabilized, the phase of stabilization is developed. Additional diseases at this stage (for example pneumonia) or additional stimuli or exercise may cause disadaptation. Consequently, the term "condition of adaptadness" was suggested by Mirsaid Mirrakhimov. In light of this definitions, the criteria of adaptadness to different altitudes and the altitudes harmful for human health were established.

The studies on effects of high altitudes and adaptation on circulatory, pulmonary and hematological system were performed under guidance of Mirsaid Mirrakhimov. The increased erythropoietin production with further hyperhemoglobinemia and erythrocytosis were revealed in residents of Tyan-Shan and Pamir, hyperglobulinemia was described in native residents of altitudes over 2500 meters above sea level; immunological changes the reduction of immune system activity were found in highlanders. This decrease in immune response in highlanders was not dependent on reduced level of allergic substances in air at high altitudes, but rather was related effects of exogenous hypoxia and increased glucocorticoid activity.

It should be noted, that these high-level basic science investigations on mechanism of adaptation of healthy humans and patients to high altitude hypoxia were accomplished upon creation of hospital in 1965 by Mirsaid Mirrakhimov and his colleagues at the Tuya-Ashu pass. The unique and single in the region high-altitude hospital is situated in Nothern Tyan-Shan at the altitude of 3200 m above the sea level, about 130 km away from the capital of republic Bishkek. The work at hospital was not only limited by scientific investigations. Several thousands of patients with coronary pathology, bronchial asthma and other respiratory diseases, cytopenia disorders, including aplastic anemia, thrombocytopenia, iron deficiency anemia; allergic diseases, including allergic rhinitis, dermatitis; functional neurological impairments have been effectively treated at this hospital with capacity of 30 beds and modern clinical and scientific equipment.

The special practical importance has studies on so-called postadaptation or deadaptation. It was established, that after descent, despite the cease of unfavorable high-altitude factors influence, the higher resistance to exogenous hypoxia, acquired as a result of high-altitude training and controlled by duration of endurance to severe hypoxic environment in bar chamber (7500 m above the sea level) and increased PWC170, are preserved for at least 6 months after descent. This work was conducted in collaboration with the Institute of Medico-Biological Problems, Moscow, Russia. This sign of relatively steady trace of adaptation was defined by Mirrakhimov as the manifestation of vegetative memory.

The increase of human endurance to different extreme factors and preservation it after adaptation period, allowed to recommend high-altitude training for health purposes. These investigations carried out with scientists from the Institute of medico-biological problems allowed to recommend use of high-altitude adaptation in astronauts to increase human endurance to different extreme factors (hypoxia, hot temperature, low physical activity, acceleration).

It was shown that after 40-day stay at the level of 3200 meters above the sea level the endurance to acute hypoxia increases; the endurance during dose physical exercises, radial acceleration, endogenous hypothermia, induced by physical activity in people wearing special isolation clothes the integrated activity of physiological functional systems become more economic in view of energy spending. This approach allowed establishing scientific criteria of selection of people to work at high-altitudes and it is being accomplished at the mining plant Kum-Tor, situated at high altitudes.

The important part of studies by Mirrakhimov and his colleagues is devoted to the physiology and pathology of permanent residents of high-altitudes. They established the normal values of laboratory and functional parameters. Their studies on respiratory system regulation in highlanders showed the changes in carotid receptors functions, which enable the emergency adaptation of ventilation of sudden changes in gas environment, and found that apnea is one the causes of arrhythmias in highlanders. He and his colleagues established the criteria for diagnosis and modern treatment approaches of life-threatening high altitude pathologies as high-altitude acute pulmonary edema, brain edema, and severe forms of mountain diseases. In 1965, for the first time in republic Mirrakhimov and his colleagues (Kudaiberdiev Z and Yusupova NYa) described 4 cases of acute high-altitude pulmonary edema developed in 4 healthy men at the Tuya-Ashu pass 3200 meters above the sea level.

Mirrakhimov further defined the high-altitude pulmonary hypertension, which signs appear at the altitude 2200-2500 meters above the sea level in part of highlanders. Right heart involvement with right ventricular (RV) hypertrophy, right atrial enlargement, conduction disturbances, were detected by electrocardiography, vectorcardiography and echocardiography in most of highlanders residing at 3000-3600-4200 meters above the sea level. It was found, that progressive right heart failure and arrhythmias develop in 4-6% of highlanders residing at altitudes 3200-3600 meters above the sea level. Most of these patients suffering from decompensated high-altitude cor pulmonale die within five years. The syndrome of night apnea, which is common in highlanders, contributes to the progression of heart failure. The thickness of right ventricular anterior wall on echocardiography exceeds 7 mm and is accompanied by dilatation of right ventricle. The physical capacity of such patients is reduced.

Further studies on the adaptation criteria of right heart in high altitude pulmonary hypertension conducted by the colleagues of Mirrakhimov at SRL and NCCT allowed to establish criteria for diagnosis of high-altitude heart: pulmonary hypertension with and without RV dilatation/hypertrophy accompanied by good quality of life and satisfactory exercise endurance are signs on adaptive changes in RV. If highlanders have changes in RV without obvious signs of RV congestive heart failure, but have low exercise capacity during bicycle test with signs of right atrial overload the compensated high-altitude cor pulmonale is diagnosed. When symptoms and signs of right heart failure appear, the decompensated high-altitude cor pulmonale should be thought. In some highlanders the adaptive changes in RV may gradually deteriorate to high-altitude cor pulmonale (compensated and decompensated) thus necessitating yearly medical examinations, including elcetrocardiographic recordings

The recent studies on mechanisms of high-altitude pulmonary hypertension development conducted by Mirrakhimov and associates showed that adrenoreceptor regulation of pulmonary arterial bed changes in high-altitude pulmonary hypertension manifesting by desensitization of beta-adrenoreceptors. The hyperreactivity of pulmonary vessels and pulmonary hypertension are associated with increased activity of smooth muscle calcium channels. The cell protein-hypoxins were described and identified for the first time. The unique cells causing injury of pulmonary arteries were found, and for the first time the unknown mitogenic protein factors, playing role in the pathogenesis of pulmonary hypertension were described. Genetic studies revealed the

relationship between presence of angiotensin-converting enzyme genotype alleles I and I/I with severity of high-altitude pulmonary hypertension and hypertensive response to exogenous hypoxia in bar chamber. Calcium antagonists of new generation (amlodipine and isradipine) were found to effectively reduce pulmonary arterial pressure and suppress the hypereactivity of pulmonary vessels to hypoxia in highlanders. Another vasodilator- 5 -phopshodiesterase inhibitor- sildenafil was shown to be highly effective in the treatment of high-altitude pulmonary hypertension with selective effects only on pulmonary circulation, not systemic.

The main results of scientific works of Mirsaid Mirrakhimov are published in form of numerous books and monographs, and papers in international core journals.

Concluding the invaluable activity of Mirrakhimov in the area of high-altitude medicine, one should remark the great role of his scientific contributions in development and welfare of our mountainous country, strengthening of health and improvement of quality of life of people. Professor Mirsaid Mirrakhimov devoted his life to this purpose, recognizing and understanding the importance of development of fundamental investigations in the area of molecular and cell biology for the future of our country, its growth and well-being.

Ryskul B. Kydyralieva, Aynagul S. Djumagulova
M.Mirrakhimov National Center of Cardiology and Therapy, Ministry of Health, Bishkek,
Kyrgyz Republic

Erratum (author's notice):

"Echocardiographic images in figures 4, 6a and 6b in Dr. Buckberg's manuscript on septal myocardial protection (Buckberg GD, Athanasuleas CL, Saleh S. Septal myocardial protection during cardiac surgery for prevention of right ventricular dysfunction. Anadolu Kardiyol Derg 2008; Suppl 2: 108-16.) come from the collaborative analysis of Aman Mahajan M.D., who collaborated in these efforts."