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THE HISTORY OF THE EMERGENCE AND POSSIBILITIES OF CARBOXYTHERAPY (CO2) IN MEDICINE

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Abstract

Today, medicine, thanks to the centuries-old experience of doctors, pharmacists and chemists, has a huge arsenal of drugs for the pharmacotherapy of various diseases. Many modern drugs, in the course of their long-term use, have expanded their therapeutic capabilities, which allowed doctors to use them in more advanced dosage forms or for the treatment of other diseases for which they were not originally prescribed. Thus, in modern medicine, carbon dioxide has been widely used for the treatment of diseases for more than 50 years, as it is an innovative, modern, polyetiological, and polypathogenetic option for off-label therapy that complements the prevention and treatment of many diseases. Today carboxytherapy is an affordable, safe, and low-cost procedure for improving the body, the purpose of which is to stimulate metabolic processes, restore the balance of tissue interactions, i.e. optimization of the body's self-regulation processes. The mechanisms of CO2 influence on biochemical and physiological processes are diverse, providing a variety of local and resorptive pharmacological effects. For diseases in dermatology, cosmetology, orthopedics, cardiology, surgery, gynecology, urology, neurology, balneology and rehabilitation of patients, carboxytherapy is an empirical method of treatment and is not considered a substitute for traditional therapy.

Keywords: *carbon dioxide, dry CO2 baths, carboxytherapy.*

Today, medicine, thanks to the centuries-old experience of doctors, pharmacists and chemists, has a huge arsenal of drugs for the pharmacotherapy of various diseases. Many modern drugs, in the course of their long-term use, have expanded their therapeutic capabilities, which allowed doctors to use them in more advanced dosage forms or for the treatment of other diseases for which they were not originally prescribed [22,13,29, 33, 15]. Of the huge number of drugs used in clinical practice, about 30-40% appeared due to the knowledge and experience of doctors who used them in the last and before last century, for example, cardiac glycosides, narcotic analgesics and derivatives of salicylic acid and many others. One of biologically active molecules, the use of which has been known for a long time, is carbon dioxide [23, 32]. Carboxytherapy, as a method of pharmacotherapy, has a centuries-old tradition, as mineral and thermal waters containing carbon dioxide were used to treat joint diseases, symptoms of ischemia and hypoxia, as well as for rejuvenation as early as in ancient times [24]. In addition, carbon dioxide was the first gas to be used in medicine [12].

The emergence of the name carbon dioxide has an interesting history and its name, which we are accustomed to, did not appear immediately. In the 16th century, it was called sour spiritus, then forest gas, fixed gas. In 1785, I. Prokhazka gave CO_2 the name mephitic gas (Mephitis was the ancient goddess who protected from harmful vapors) [39].

Since 1720, carbon dioxide has been used with success at the Pyrmont resort in Germany. 100 years later (1819) K. Heidler published the first scientific works on the positive effect of carbon dioxide on the human body. At well-known Czech spas (Karlovy Vary and Maryanovské Lazne), after 1946, carbon dioxide injections were first used. Consequently, the emergence of carboxytherapy did not arise out of nowhere. Since it has long been known that the mechanism of hypoxia formation is associated not only with a lack of oxygen, but also carbon dioxide. Hemoglobin gives oxygen to tissues only in exchange for carbon dioxide. This phenomenon was discovered at the end of the 19th century by the Russian scientist B. Verigo and the Dane K. Bohr independently of each other [14].

Consequently, carboxytherapy began its centuries-old use in medicine from mineral carbon dioxide baths, which in turn was taken from ancient medicine. However, in the XIV-XX centuries, carbon dioxide was used mainly in resorts in the form of baths with CO_2 and drinking mineral bicarbonate water. In 1981, a technique for the medical use of carbon dioxide called "Bioterica" was developed and patented, and it provides for the use of carbon dioxide in the form of dry baths. The term carboxytherapy was coined in 1990 when the Italian Ministry of Health first certified carboxytherapy as an outpatient treatment, with an alternative name for this method - "pneumopuncture" or "gas injections". These terms are still used today in medicine. In 1993, a universal apparatus for controlled injection of carbon dioxide was created, and in 1994, at the Institute of Cardiovascular Pathology at the Roya Medical Spa, about 20 thousand patients with cardiovascular pathologies successfully underwent transdermal CO_2 therapy. In 1996, CARBOMED device was created, patented and certified as a medical device for injection with an electronic regulator of carbon dioxide flow, and now this device is widely used in many countries of the world [27].

Today, the therapeutic potential of this method of treatment is provided by the following procedures: non-invasive carboxytherapy ("dry" and water carbon dioxide baths, cosmetic carbon applications and deep breathing stimulants), as well as modern methods of invasive carboxytherapy [19]. In clinical medicine, CO_2 has long been used as a stimulator of the respiratory center (about3-5% CO_2 is part of the respiratory mixture - carbogen). This pharmacological effect is also repeatedly mentioned in many author's methods (breathing according to KP Buteyko, VF Frolov's simulators, etc.), in addition, it is also used for CO_2 lasers [17]. Consequently, the use of CO_2 in medicine lasts for many centuries. At first, it was carried out empirically, but gradually this experience moved to a broad clinical evidence base. Today, scientific publications with evidence of the practical use of carboxytherapy for the treatment of many pathological conditions are constantly appearing in the world [10].

Starting from the 60s of the last century, and especially often in the last 20 years, publications began to appear on the use of CO_2 in angiology, rheumatology (arthritis), urology, dermatology

(keloids, psoriasis vulgaris, scleroderma, ulceration of various origins), in sports and aesthetic medicine [18, 1]. An important role in the introduction of carboxytherapy is played by the Center for the Study of the Results of Carboxytherapy in the Field of Microangiology and Microcirculation at the University of Milan, as well as similar centers in Austria, Hungary, France, Czech Republic, Slovakia and the USA. There is an international society and schools "GISCT - International Scientific Carbon dioxide Therapy Group" and "International School of Carboxytherapy". The main purpose of these research institutions is to foster ongoing research into the carboxytherapy method in accordance with the principles of evidence-based medicine.

The most widespread use of carbon dioxide in medicine, primarily found in resort medicine, where carboxytherapy is known as "gas injections" for the treatment of joint diseases, in violation of blood supply in patients with diabetes mellitus, as well as for the treatment of patients with cardiovascular diseases [32, 27]. In recent years, this method has been widely used in dermatology, aesthetic dermatology, and anti-aging medicine. The method of carboxytherapy has been mastered and is successfully applied in leading clinics in Western and Central Europe, as well as in leading European resorts in France, Germany, Czech Republic, Slovakia, Ukraine, and many other countries of the world. In therapeutic cosmetology in Europe, 2012 has been declared the year of carboxytherapy. Currently, the use of various therapeutic modifications involving CO_2 is included in the usual list of procedures not only in hospitals and rehabilitation departments but also in the offices of plastic surgeons, dermatologists, orthopedists, spa centers, beauty salons, and other medical institutions [9, 2528, 3, 4, 16, 21].

Since 2013, the Department of Pharmacology of the National University of Pharmacy (Kharkiv, Ukraine) has been conducting preclinical experimental substantiation of the carboxytherapy method in order to identify the features of the anti-inflammatory, analgesic, antioxidant effects of CO_2. Professor of the Pharmacology and Pharmacotherapy Department S. M. Drogovoz and her students have published more than 50 scientific articles, made more than 20 reports at congresses, conferences of pharmacologists, pharmacists, and therapists, on pharmacodynamics, the mechanism of action, and indications for the use of carboxytherapy. Since 2015, the method of carboxytherapy in Ukraine has become an alternative method of treatment for many diseases, due to its safety and high efficiency [27].

Thus, today it has been proven that carbon dioxide is essential for the body, like oxygen, since it is an active physiological stimulator of many processes and when it is deficient, tissue hypoxia, metabolic disorders and spasms of vascular smooth muscles occur, which leads to the development of arterial hypertension, ischemia, obesity, diabetes and other diseases [32].

Having found out that carbon dioxide in the body is a "watchdog" signaling the danger of hypoxia, they began to use it for respiratory depression during anesthesia and add it to scuba divers' gas mixtures to stimulate the respiratory center. The content of CO_2 in the blood affects oxygen binding with hemoglobin and its ability to ingress into tissues, as well as maintaining a stable acid-base balance (pH) in the body. However, one of the main physiological effects of carbon dioxide is its stimulating action on the chemoreceptors of the respiratory and vasomotor centers of the medulla oblongata. As a result, breathing deepens and quickens, tissue respiration increases, coronary dilatation occurs, stroke and cardiac output increases, myocardial and central nervous system ischemia decreases, CO_2 stimulates immunogenesis, reparative processes in the inflammation zone, and mental performance increases [32].

Consequently, CO_2 in physiological concentration is necessary for the normal functioning of the body: regulation of cellular respiration, maintenance of homeostasis, acid-base balance, angiogenesis and immunity, the normal course of all biochemical, humoral and tissue processes. In addition, the uniqueness of the physiological value of CO_2 is determined by the fact that it participates in the reactions of biosynthesis of the most important components of the cell: lipids, carbohydrates, proteins, nitrogenous bases of nucleotides, and hence nucleic acids. A decrease in the concentration of CO_2 in the body below 4% leads to its death, as oxygen starvation sets in, which changes the activity of enzymes and the rate of all biochemical reactions

of the body [8]. Therefore, CO2 paired with oxygen effectively function in our body: the cells of animals and humans need about 6-8% CO2, and 2% O2 in relation to their content in the inhaled air. In this case, oxygen is an agent oxidizing organic substances in the process of energy generation, but when the oxidation process is incomplete, toxic products are formed - reactive oxygen species (free radicals). They are the main trigger mechanism of aging, disrupting the subtle and complex biochemical intracellular processes of the body. While carbon dioxide reduces the rate of oxidative reactions and thus exhibits antioxidant properties, contributing to the "antiaging" effect, on the other hand, prolonged hypocapnia and hypoxia can serve as a trigger for pathological processes in the body [27].

From a physiological point of view, CO2 in the body is a natural regulator of respiration, blood circulation (the pH of blood plasma depends on the ratio of the concentration of carbon dioxide and bicarbonate ions dissolved in it), metabolism, electrolyte balance, acid-base balance, the excitability of nerve cells, and smooth muscle tone (bronchi, blood vessels, urinary tract). Bicarbonates stimulate the secretion of hormones from the pancreas (insulin) and gonads (testosterone and estradiol); enhance the metabolic processes of the body: carbohydrate, fat, protein, electrolyte. This refutes the outdated concept of CO2 as a "toxin" that is rapidly excreted from the body [11]. In addition, CO2, participating in the distribution of sodium ions, affects the permeability of cell membranes of neurons and the excitability of nerve cells, helps to reduce stagnant foci in the cerebral cortex. CO2 accelerates the processes of elimination of toxins, neocollagenogenesis (enhances the synthesis of elastin, collagen, and hyaluronic acid). Relaxes spasmodic muscles, inhibits pain sensitivity [27].

In surgery for performing abdominal operations using artificial organs, carbon dioxide is used mainly to create atmospheric conditions in the wound close to physiological. Another area of its use in surgery is the use of CO2 for endoscopic laparoscopic operations (injection of CO2 into the abdominal cavity in order to increase the area of the operating field for viewing). Also, the "pillow" of carbon dioxide protects the surgical wound from drying out tissues, being a synergistic support for healing after the use of skin implants, conditions after carpal tunnel surgery, Dupuytren's contracture. A CO2 laser is used during surgery as a scalpel to remove warts and papillomas. After such a procedure, in contrast to the usual incision with a scalpel, there are practically no marks on the skin. The incision with the CO2 laser is made much thinner and the bleeding is stopped by the CO2 beam. In addition, in surgery and cosmetology, an ablative CO2 laser is used to smooth out scars on the skin, and in ENT surgery for the treatment of epithelial dysplasias, laryngeal tumors, snoring (sometimes in 1 session), when removing polyps in the nose, tonsillectomy and laryngeal stenosis. [35, 26, 34].

Today, carboxytherapy is an alternative method in the complex treatment of diseases of the cardiovascular system. Such pathologies include ischemic heart disease: angina pectoris, myocardial infarction in the recovery phase (to improve coronary blood flow; normalize metabolic processes in the myocardium); heart defects; hypertension 1, 2 stages outside the crisis, symptomatic arterial hypertension; neurocirculatory dystonia in hypotensive, cardiac, arrhythmic and mixed types; obliterating atherosclerosis of the vessels of the lower extremities, thrombangitis, thrombophlebitis in remission; telangiectasias (spider veins), Raynaud's and Burger's syndromes, endarteritis, lymphatic and venous edema, atherosclerosis, acrocyanosis. By increasing the rate of lymphatic drainage, carboxytherapy brings positive results in lymphedema (a condition accompanied by increasing soft tissue edema) [31, 30].

In diseases of the respiratory system, carboxytherapy helps reducing the complex of symptoms in chronic and spastic types of bronchitis, bronchial asthma, pneumosclerosis, pulmonary emphysema, silicosis due to its anti-inflammatory, antihypoxic, antioxidant, antispasmodic, antiseptic, antiallergic properties [4, 32, 5].

In metabolic disorders and endocrine diseases, indications for carboxytherapy are exogenous constitutional obesity of stages I-III, diabetes mellitus (mild and moderate), hypothyroidism with the presence of myocardial dystrophy, metabolic syndrome. In patients with diabetes, under conditions of persistent hypoxia, the biochemical process of oxidative phosphorylation is uncoupled,

which is accompanied by serious manifestations of tissue hypoxia. It was found that carbon dioxide increases the degree of conjugation of tissue respiration and phosphorylation, disturbed during the pathological process in the cell [7].

Clinical observations have shown that the use of carboxytherapy in the form of dry CO2 baths not only contributed to a decrease in fasting glycemia but also had a normalizing effect on the parameters of glycosylated hemoglobin and glucose during the postprandial test. The symptomatic positive effect of carboxytherapy was expressed in a decrease in hyperglycemia, thirst, symptoms of polyuria, itching of the skin, and weakness. Dry carbonic baths stimulate antistress systems, eliminate the imbalance of autonomic regulation and increase the nonspecific resistance and adaptive capabilities of the body, which is especially important for patients with discirculatory encephalopathy due to the small vessels impairment in diabetes mellitus [38].

Consequently, carbon dioxide baths have a large arsenal of metabolic effects that have a universal normalizing effect on the course of pathological processes in diabetes. Scientists in the United States proposed to treat allergies by inhaling carbon dioxide, explaining that due to the above properties of CO2, the production of calcitonin is stimulated, which is involved in the mechanisms of allergy development by reducing inflammation.

Gynecology has long used invasive carboxytherapy and a special pulsed CO2 fractional laser as an adjunct treatment for vulvovaginal atrophy, amenorrhea or oligomenorrhea; to slow the signs of sexual aging; with therapeutic and diagnostic laparoscopy; when removing papillomas, genital warts, carcinomas; treatment of cervical erosion, leukoplakia; with polycystic, endometriosis, menopause and the initial stage of stress urinary incontinence. Invasive carboxytherapy in gynecology is used for pain in the lower abdomen (painful periods, synechias after surgery) [20].

In balneology, CO2 baths are recommended as an additional alternative method for the following diseases of the reproductive system: impotence, chronic inflammatory diseases of the female genital organs in remission (adnexitis, salpingo-oophoritis, menopause) [2].

In proctology, there is an experience in the use of carboxytherapy in the treatment of anal fissures; in urology and nephrology in diseases of the kidneys and urinary system: in chronic prostatitis and pyelonephritis, BPH, i.e. with violations of blood flow and hypoxia of the kidneys and pelvic organs. A good effect is achieved when using carboxytherapy in patients with Peyronie's disease by improving their condition and sexual activity. Due to its anti-inflammatory, antioxidant, antihypoxic, anti-ischemic properties, carboxytherapy is able to influence the pathogenesis of these diseases by improving blood circulation in the pelvic region, reducing the symptoms of diseases of the genitourinary organs and significantly improving the quality of the sexual life of these patients [36, 37]

Thus, in modern medicine, carbon dioxide has been widely used for the treatment of diseases for more than 50 years, as it is an innovative, modern, polyetiological, and polypathogenetic option for off-label therapy that complements the prevention and treatment of many diseases. Today carboxytherapy is an affordable, safe, and low-cost procedure for improving the body, the purpose of which is to stimulate metabolic processes, restore the balance of tissue interactions, i.e. optimization of the body's self-regulation processes. The mechanisms of CO2 influence on biochemical and physiological processes are diverse, providing a variety of local and resorptive pharmacological effects. For diseases in dermatology, cosmetology, orthopedics, cardiology, surgery, gynecology, urology, neurology, balneology and rehabilitation of patients, carboxytherapy is an empirical method of treatment and is not considered a substitute for traditional therapy. Today carboxytherapy is a vivid example of an off-label prescription of drugs, since carboxytherapy, without the results of its wide preclinical studies, is used in all fields of medicine and has become a universal and safe method of complementary and alternative therapies for most diseases. In addition, carboxytherapy can lead to the innovative use of drugs in many areas of medicine without a wide preclinical study and without its inclusion in the recommended dosage forms, treatment protocols, reference books, textbooks, thanks to its rich pharmacodynamics, harmlessness, and 50 years of effective experience of its use.

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