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MODERN PHARMACOLOGICAL ALTERNATIVES IN CARDIOLOGY

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Abstract

Diseases of the cardiovascular system (CVD) in terms of severity and prevalence occupy one of the leading places among pathologies. So in the ICD-10 (International Classification of Diseases), there is a large arsenal of diseases associated with dysfunction of the heart and blood vessels. A similar trend can be traced in ATC (anatomical and therapeutic classification of drugs), in which the arsenal of drugs for the treatment of CVD is constantly increasing. However, ATC lacks options for alternative therapeutic care for CVD diseases from the modern experience of carboxytherapy (CO_2 treatment) and off-label therapy (usage of drugs outside the label). Over the past 20-30 years, these types of therapies have gained extensive global experience, including in cardiology and angiology. Thus, carboxytherapy and off-label therapy are alternative therapies in cardiology. With any variant of carboxytherapy application, the same self-regulation mechanisms are activated in different sequences and intensities, leading to the restoration of homeostasis: the function of external respiration improves, and the vascular tone is simultaneously regulated. Strengthening blood flow and normalizing the rheological properties of blood eliminates venous stasis, mobilizes anaerobic energy metabolism, and reduces oxygen consumption by the heart muscle. Therefore, as long as the physician is convinced that the drug will be safe and effective for the patient, he can prescribe this drug as an off-label therapy.

Keywords: CVD, *carboxytherapy, off-label therapy, cardiology.*

Diseases of the cardiovascular system (CVD) in terms of severity and prevalence occupy one of the leading places among pathologies [11, 22, 17, 26]. So in the ICD-10 (International Classification of Diseases), there is a large arsenal of diseases associated with dysfunction of the heart and blood vessels. A similar trend can be traced in ATC (anatomical and therapeutic classification of drugs), in which the arsenal of drugs for the treatment of CVD is constantly increasing. However, ATC lacks options for alternative therapeutic care for CVD diseases from the modern experience of carboxytherapy (CO_2 treatment) and off-label therapy (usage of drugs outside the label). Over the past 20-30 years, these types of therapies have gained extensive global experience, including in cardiology and angiology [14, 21, 5, 6, 15, 10, 27, 20, 9].

Over the years, the vessels and the heart undergo age-related and pathological changes, because of this, they are not able to provide organs and peripheral tissues with the necessary amount of oxygen, due to which hypoxia and ischemia occur [25, 2]. To stop these processes, it is first of all necessary to provide cells with oxygen. Invasive and non-invasive carboxytherapy are aimed precisely at solving the problem of hypoxia [5, 27, 9]. In addition, the use of carboxytherapy for CVD helps to dilate small arteries, capillaries, improve blood circulation and oxygenation of organs, including the heart, and increase its resistance to physical stress [18].

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. Due to the main hemodynamic, tissue, and biochemical mechanisms of action, CO_2 is one of the humoral factors that ensure a constant tone of the respiratory and vasomotor centers, as well as due to the interaction of its central and peripheral mechanisms, direct and reflex action. As a result, breathing deepens and quickens, tissue respiration increases, coronary dilatation occurs, stroke and cardiac outputs increase, myocardial and central nervous system ischemia decrease [24, 29, 12].

Due to the direct and reflex action of CO_2 on the vasomotor center of the medulla oblongata, blood is redistributed in the body, peripheral vessels dilate, and anaerobic energy metabolism is mobilized. As a result of these processes, the lumen of peripheral vessels is regulated, venous outflow and basal tone of arterioles are normalized, coronary dilatation, stroke, and cardiac outputs change, which increases blood flow and leads to redistribution of blood in the body and improvement of tissue oxygenation. As a result of these effects, myocardial hypoxia decreases, exercise tolerance increases, diastolic pressure, and heart rate decrease [27, 3].

The vasodilation effect is also associated with the direct action of CO_2 on angioreceptors and with the release of vasoactive compounds: histamine, acetylcholine, serotonin, and kinins. This effect of CO_2 on blood vessels leads to dilatation of coronary vessels, bradycardia and a decrease in blood pressure (BP), improvement of tissue tropism. CO_2 also stimulates neoangiogenesis and normalizes blood viscosity [1].

Oxygen starvation in tissues causes hypoxia, which is always accompanied by hypercapnia. To eliminate hypoxia, many European and American clinics use a method based on the homeopathic principle "from the opposite" - offering carboxytherapy as an alternative treatment: with the introduction of CO_2 subcutaneously, intradermally, inhalation, or transdermally, the effects of oxygen starvation are eliminated by creating artificial hypercapnia in the tissues, which in its turn causes vasodilation with increased oxygen delivery to the body [4]. In this case, the mechanism of regulation of CO_2 and O_2 gas exchange in the body is provided by the synchronization of several processes: due to the implementation of humoral, biochemical, and tissue mechanisms of carboxytherapy [27].

The diffusion capacity of CO_2 in the "alveoli - capillary" system is 25-30 times higher than that of O_2 and does not stop in the alveoli even when external respiration stops. A similar process takes place in the organs of the cardiovascular system, where the gas exchange $O_2 \boxed{\leftrightarrow} CO_2$ also takes place through continuous diffusion [4]. This mechanism of action of carboxytherapy is associated with an increase in tissue oxygenation and is due to the Verigo-Bohr effect: the influence of CO_2 concentration and pH on the process of binding and releasing O_2 from hemoglobin. This process of CO_2

and O2 gas exchange occurs both in the lungs and in other organs [3, 27]. Since carbon dioxide is the most important product of cellular respiration, many sensors in the body regulate the concentration of this gas. A shift in the level of CO2 in any direction from physiological values triggers numerous adaptation reactions.

The cells of the body (cardiomyocytes, neurons, hepatocytes, etc.), regardless of their functions, emit CO2 as the end product of biochemical reactions. The process of removing CO2 from the body through the lungs contributes to an increase in hemoglobin oxygenation: the removal of one part of CO2 increases the oxygen concentration in the tissues more than 3 times. These mechanisms of CO2 action are widely used in medicine for inflammatory and other diseases accompanied by hypoxia and edema [27]. Since CO2 is a powerful natural vasodilator (it lowers the basal tone of arterioles, which contributes to increased blood flow), the body interprets carboxytherapy as oxygen deficiency and reacts by increasing not only blood flow but also vascular endothelial growth factor, which stimulates neoangiogenesis, therefore, carboxytherapy also improves blood supply due to the appearance of new vessels of the brain and heart [7, 8].

The mechanism of action of CO2 with an external (transdermal) application (bath) has been studied sufficiently. Its effect on the body, including the joints, includes mechanical, thermal, and chemical factors, each of which has a specific effect due to the multifunctionality of CO2. The peculiarity of the mechanical action of such baths is the irritation of the skin receptors with CO2 bubbles, and the chemical irritation of the receptors, which contributes to the formation of active biological substances. It was found that during a CO2 bath lasting 10-15 minutes up to 20-25% of carbon dioxide penetrates through the skin [28]. The biochemical effect of carbon dioxide baths also lies in the fact that with an increased concentration of CO2 in the blood, a cascade of reactions is activated that improve oxygenation and energy supply to all tissues of the body.

Afferent impulses from chemoreceptors of the skin also excite the centers of the medulla oblongata and cause pronounced visceral reactions: the parasympathetic effects of CO2 on the heart increase. This leads to increased coronary dilation and the development of coronary collaterals. At the same time, the consumption of O2 by the heart muscle decreases by 18-22%. As a result, myocardial ischemia decreases - the main link in the pathogenesis of coronary heart disease, exercise tolerance increases, diastolic pressure, and heart rate decrease [23, 13].

Consequently, carbon dioxide baths affect, on the one hand, the autonomic regulation of the CVS organs (reduce sympathetic vasoconstrictor effects, slow down the rhythm of cardiac activity, and prolong myocardial diastole), on the other hand, they affect the capacitive parameters of the vessels due to the direct and reflex action of CO2 (vasodilatation). These mechanisms contribute to a decrease in myocardial demand for O2 while increasing its delivery to organs (the Verigo-Bohr effect) and enhancing the processes of gas exchange and microcirculation [4, 29].

Along with solving local problems, CO2 has a systemic effect on the body: sympatholytic, muscle relaxant, analgesic, anti-inflammatory, antioxidant, rheological, and by increasing the level of tissue oxygenation, it improves tissue tropism and the protective properties of the body. The ability of carboxytherapy to affect an extensive pathological symptom complex can be explained by the participation of CO2 in many metabolic and reflex processes of systemic self-regulation since CO2 acts as a biochemical pacemaker that triggers cascades of mechanisms of all body systems (respiratory, cardiovascular, excretory, hematopoietic, immune, humoral, etc.) [5, 19, 27].

CO2 acts on the vascular tone sequentially, but in opposite directions: first, CO2, reflexively stimulating the vasomotor center through chemoreceptors, increases blood pressure; secondly, CO2 lowers blood pressure, exerting a direct vasodilator effect. As a result, there is a redistribution of blood in the body with the dilation of peripheral vessels (CO2 is a strong peripheral vasodilator), venous outflow normalizes, coronary vessels dilate, myocardial circulation improves, and the minute volume of blood increases. Due to the reflex multilateral impulse and resorptive action of CO2, the following occurs: a decrease in the tone of preterminal and terminal arterioles and capillaries; oxygenation, neocollagenogenesis, vascularization

are improved; blood viscosity decreases; blood and lymph circulation, filtration processes in the renal glomeruli increase, swellings decrease [30, 31].

Thus, carboxytherapy, due to the polypathogenetic pharmacodynamics of CO2, is an effective and safe method of treating many CVD diseases. For more than 50 years, CO2 has been widely used in medicine for the treatment of CVD diseases, being a polietiologic and polypathogenetic option of off-label therapy, complementing the prevention and treatment of many diseases of the heart and blood vessels.

Today carboxytherapy as an off-label method is an alternative in the complex treatment of diseases of the cardiovascular system without a wide preclinical study and its inclusion in the recommended drug formularies, treatment protocols, reference books, textbooks, thanks to its rich pharmacodynamics, harmlessness, and 50 years of effective experience of its off-label applications in wide medical practice.

Off-label therapy is common in medical and pharmaceutical practice worldwide and is recognized when other treatments are ineffective or unavailable. Currently, many countries have legislation related to the off-label use of drugs: Germany, the United Kingdom, France, Japan, Italy, the Netherlands, New Zealand, India, Ireland. Off-label use is a common clinical practice in China and the USA [6, 10, 15].

Consequently, off-label therapy is part of clinical practice around the world and remains generally recognized in world health care and, in particular, in cardiology and angiology.

An example of off-label therapy in cardiology is aspirin, which was used to reduce the risk of heart attack for several years before this efficacy was confirmed in clinical trials. For decades, doctors have prescribed aspirin off-label to reduce the risk of heart attacks (as a cardioprotective agent), but the FDA did not approve such use until 1998. There are reports of the effectiveness of the use of this drug off-label for the prevention of coronary heart disease in patients with diabetes mellitus. The "journey" of aspirin to its current position is long and still incomplete. In addition to its thrombolytic effect, its antitumor potential is still being studied, in particular in colon cancer [32, 33, 34].

The synthetic antioxidant N-acetylcysteine (NAC) belongs to mucolytic drugs for the treatment of acute and chronic diseases of the bronchopulmonary system. Today, the cardioprotective effect of this drug is being actively studied, in particular, in 2017, in a randomized, placebo-controlled, multicenter clinical study, it was revealed that intravenous injections of NAC (29 g), together with low-dose nitroglycerin (7.2 mg), contributed to a significant reduction in the zone of myocardial infarction. An analysis of clinical and experimental studies indicates that the use of NAC off-label is promising for the treatment of diabetic cardiomyopathy in patients with type 1 diabetes [35, 36].

Since Viagra, a blockbuster of erectile dysfunction treatment can dilate arteries enough to lower blood pressure, it is used off-label to treat pulmonary hypertension, heart failure, and diastolic dysfunction as well as Raynaud's disease. It is also known that this drug thins the blood in the vessels by increasing the level of the signaling substance nitric oxide [37].

Pulmonary hypertension is a rare vascular disease in which the lungs cannot provide adequate oxygen to the body. Drug therapy for newborns with this disease is represented by a small number of registered drugs. Knowing that nitric oxide deficiency is one of the causes of pulmonary hypertension, doctors use inhalations of nitric oxide in this disease. However, nitric oxide is expensive, which is why pediatricians prescribe Viagra off-label in the hope that it can provide better and longer-lasting results.

It has long been known that antidepressants due to cardiotoxicity are contraindicated in patients with diseases of the circulatory system. An exception is the new serotonin reuptake inhibitors: they have been proven to have no cardiotoxic effect. However, little was known about the efficacy and safety of their use in patients with coronary artery disease. The results of Pfizer's "Sertraline Antidepressant Heart Attack Randomized Trial" have shown that patients who received sertraline off-label had a 20% reduction in cardiovascular complications [38].

Since 1970, indomethacin has been used for therapy to close persistent, symptomatic patent ductus arteriosus in newborns. Therefore, it has

become the off-label drug of choice for many neonates to prevent surgery [39].

After the approval of amiodarone, it was widely used off-label, mainly for the treatment of atrial fibrillation. The frequency of such off-label administration of amiodarone is about 80% (i.e., the proportion of its use on-label is only 20%), but it should only be used off-label for "life-threatening arrhythmias for which no other treatment has been effective" [40].

The indication for losartan is the treatment of arterial hypertension, chronic heart failure (as part of combination therapy with diuretics and cardiac glycosides), especially in case of intolerance to ACE inhibitors. In addition to the antihypertensive effect, the cardioprotective effect of off-label losartan in myocardial fibrosis is being actively investigated [43].

Magnesium sulfate is used off-label for many indications: it lowers high blood pressure, has a prophylactic effect in thrombosis [41, 42].

Retrospective studies have proven the efficacy of off-label paracetamol (Panadol) to close the patent ductus arteriosus (Botalli). After the administration of the drug orally (at a dose of 15 mg/kg every 6 hours), closure of the ductus arteriosus was achieved within 48 hours in all children to whom it was administered. At the same time, the toxicity of the drug was not observed [44, 45].

Table 1 shows off-label drugs that are used for CVD diseases.

Thus, carboxytherapy and off-label therapy are alternative therapies in cardiology. With any variant of carboxytherapy application, the same self-regulation mechanisms are activated in different sequences and intensities, leading to the restoration of homeostasis: the function of external respiration improves, and the vascular tone is simultaneously regulated. Strengthening blood flow and normalizing the rheological properties of blood eliminates venous stasis, mobilizes anaerobic energy metabolism, and reduces oxygen consumption by the heart muscle. Therefore, as long as the physician is convinced that the drug will be safe and effective for the patient, he can prescribe this drug as an off-label therapy.

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Table 1. The off label use of drugs in cardiology and angiology

Disease/symptom/syndrome	Off-label drugs
Anemia	Fentanyl (Actiq)
Hypertension	Acetylsalicylic acid, warfarin, dextromethorphan, olanzapine, retigabine, sildenafil, topiramate
Atrial fibrillation	Amiodarone
Myocardial fibrosis	Atenolol, losartan
Cardioprotector, reduction of myocardial infarction area	Acetylcysteine
Thrombosis	Magnesium sulfate, metformin
Vasculitis	Methotrexate, rituximab, tocilizumab
Raynaud's disease	Prazosin, sildenafil
Congestive heart failure, diastolic dysfunction	Sildenafil
Cardiovascular complications	Sertraline (Zoloft)