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THE ROLE OF ENVIRONMENTAL FACTORS IN THE PATHOGENESIS OF CARDIOVASCULAR DISEASES PART 1. AIR POLLUTION

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ABSTRACT — Background. Many factors and mechanisms are involved in the pathogenesis of cardiovascular diseases (CVD). Among them, as recent studies show, environmental factors play a vital role. At the same time a number of modern achievements in health care, including the improvement of early diagnosis and treatment methods for CVD has not significantly affected the rates of morbidity, mortality and disability in the population worldwide. This circumstance emphasizes the need to study the influence of additional factors, including environmental factors, in the fundamental processes of CVD pathogenesis and the subsequent translation of this knowledge into clinical practice.
Goal. To study the effect of air pollution on the development and progression of cardiovascular diseases and discuss underlying causes.
Methods. Analysis of modern international literary sources indexed in the PubMed / Medline and Embase databases.
Results. Current clinical and experimental data support the relationship between air pollution with the risk of development and mortality caused by cardiovascular diseases. However, the pathophysiological mechanisms underlying this relationship are still underreported. It is believed that a vital role in the pathogenesis is played by endothelial dysfunction, increased thrombus formation, inflammatory processes and oxidative stress, which underlies the formation and progression of atherosclerosis, as well as an imbalance of the autonomic nervous system, which contributes to the development of arterial hypertension.
Conclusion. According to the study, atmospheric air pollution has a significant impact on the pathogenesis of cardiovascular diseases. There is an urgent need for a further study of the specific pathogenetic mechanisms underlying the influence of these environmental factors on the development and progression of CVD to develop further treatment and prevention strategies to minimize the negative impact.

KEYWORDS — Environmental factors; cardiovascular diseases; atherosclerosis, atmospheric air, pollution.

INTRODUCTION

Modern achievements in the diagnostics and treatment of cardiovascular diseases (CVD), such as early diagnosis and new therapeutic strategies, have not yet significantly affected the high rates of morbidity and mortality from CVD [9–11, 15, 20]. The prevalence of CVD increases steadily in countries with middle and low living standards, as well as in the developed countries. An example of this is the dynamics of static CVD mortality (coronary heart disease, heart attack, and stroke) in the United States from 1960 to 1990. CVD mortality rates gradually declined, after which there was a significant slowdown in the rate of decline. Still, shortly after, on the contrary, there was a steady rise in mortality and morbidity rates. Considering this trend by 2030, approximately 40% of the population will suffer from some form of CVD, according to experts' estimates [30, 37]. The widespread increase in morbidity and mortality from CVD and the inability to influence it significantly indicate a lack of understanding of the fundamental pathogenetic processes of CVD and insufficient attention of researchers to effects of environmental factors.

According to several researchers, human health is closely related to environmental factors [1, 2, 4]. Many diseases, including CVD, are caused by some chronic pathological processes resulting from a complex interaction between genetic predisposition and environmental / lifestyle factors, which leads to structural and functional disorders of tissues and cells of the cardiovascular system (CVS). Although the specific contribution of these factors is underresearched, there is every reason to believe that environmental and lifestyle factors play a more significant role in CVD development compared to genetic predisposition [4]. This opinion is supported by several studies, which have shown that changes in environmental factors and lifestyle can significantly affect the risk of CVD and further prognosis [1, 2, 4]. Hence, the data indicate that in most cases, it is possible to both prevent the development of CVD and improve the course and prognosis of an existing CVD by changing environmental factors and lifestyle of patients.

The purpose of this article, which is the first part of our review, is a comprehensive analysis of the negative impact of such an environmental factor as air pollution on the development and progression of CVD.

AIR POLLUTION

Our modernized environment is flooded with various synthetic chemicals and pollutants that may damage organs and tissues in the human body. According to some estimates, more than 30,000 synthetic substances are currently circulated, of which at least 5,500 are produced in significant volumes, amounting to about 100 tons per year [29]. Almost all major rivers and lakes are significantly polluted by synthetic compounds, pesticides, and heavy metal ions. However, many pesticides, including lindane, chlordane, and dichlorodiphenyltrichloromethylmethane (dust, DTT), have been found in the Canadian Rockies, human-made mercury has been found in uninhabited Arctic regions [46]. These data indicate that as a result of pollution of human habitats and the ubiquitous spread of pollutants, there are no unpolluted ("clean") places on the planet. High levels of pollutants are mainly released into the air, thus can be transported over long distances. According to research results, air pollution in many developing countries significantly exceeds the WHO standards [29, 46].

The largest contributors to air pollution are mixtures of complex aerosols containing both particles and gases. Among the contaminating particles, particulate matter (PM) is distinguished, which are divided into two peaks corresponding to large particles (10-2.5 μm) and small particles (0.1-2.5 μm), when analyzed by weight. The fine particle fraction also contains a small proportion of ultrafine particles, which, while making a modest contribution to the total PM volume, contains the most considerable amount of pollutants by quantity.

Aerosols released directly into the environment mainly consist of minerals, soot, particles of salts, pollen, and spores, while secondary aerosols are formed from sulfates, nitrates, and organic compounds. In addition to particulate matter, indoor and outdoor air contains various gaseous pollutants, including volatile organic compounds (VOCs), nitrates, nitrogen and sulfur oxides, and ozone. The WHO estimates that worldwide air pollution may be associated with 7 million premature deaths per year. Of these, 1.6 million deaths are in China and 1.3 million in India. However, in the USA, premature mortality from air pollution ranges from 55,000 to 100,000 [8, 34]. According to some data, when speaking about the mortality rates, air pollution competes with the consequences of hypertension, smoking, and lack of physical activity [12, 24]. It is unfortunate that in some developing countries of our planet, more than 95% of the urban population lives in cities that significantly exceed standards of pollution established by WHO [24]. According to a study by J. Lelieveld et al. [34], the primary sources of pollution in different geographic regions are as follows (Table). Notably, in developing countries (China and India) a significant proportion of deaths (about 10 million cases) due to air pollution were associated with domestic and commercial energy use [34]. Also, an estimated 3.54 million deaths are attributable to air pollution from biomass burning used to heat the homes.

In some other countries, particularly the United States and Western Europe, agriculture, power generation and road transport are major air pollutants. Agricultural pollution, which contributes to particulate matter of approximately 2.5 μm (PM 2.5), accounts for almost 20% of total ambient air pollution. According to the study, the mortality rate due to agricultural air pollution worldwide is approximately 6.6 million deaths [34].

Exposure to PM 2.5 is associated with approximately 70-80% of premature deaths from CVD [5]. The reasons for such a high vulnerability of organs and tissues of the cardiovascular system (CVS) to such particles remain unclear. There is evidence that even short-term exposure to polluted air is associated with myocardial infarction, stroke, arrhythmia, atrial fibrillation, and hospitalization due to exacerbated heart failure [6, 7, 24]. There is a very close relationship between chronic exposure to pollutants and the progression of atherosclerosis, impaired blood pressure regulation, increased peripheral thrombosis, as well as impaired endothelial function, and increased insulin resistance [6, 7, 14, 24, 26].

It is worth bearing in mind that air pollution has a variable effect on cardiovascular health depending on individual susceptibility and several additional factors. For example, people with pre-existing CVD, atherosclerosis or diabetes mellitus, or heavy smokers are more vulnerable to the adverse effects of air pollutants. Age, gender, ethnicity, and nutritional and socioeconomic status are important factors that influence human susceptibility to pollutants [26].

In contrast, people with good health are less prone to be affected by air pollutants. For example, an extensive study of 17,545 male workers found no correlation between CVD and long-term exposure to particulate matter. The absence of a negative impact on CVS health in these subjects was associated with a higher socioeconomic status and a healthy lifestyle [40]. However, another study reports that even young and healthy people show signs of endothelial damage and dysfunction in response to pollutants. Nonetheless, as the researchers suppose, such damage to CVS components in healthy people with a low risk of CVD can be compensated for a long time and not manifest clinically [39].

Table 1. *Premature mortality of the population of different countries, caused by various sources of air pollution. According to J. Lelieveld et al. [34]*

Source of pollution	% Worldwide mortality	% Mortality in the USA	Countries	The main constituents of polluted air
Residential (household) energy	31	6	China, India, Indonesia, Vietnam	Carbon dioxide, carbon monoxide, VOCs, nitrates, nitrogen oxides, sulfur oxide IV, mercury, PM 2.5
Agriculture	20	29	Europe, Russia, Japan, USA	Inorganic PM 2.5, ammonia, sulfates, nitrogen oxides
Power generation	14	31	USA, Russia, Korea, Turkey	Sulfates, nitrates, PM 2.5, mercury
Industrial pollution	7	6	Japan, Germany, China	Sulfates, PM 2.5, VOCs, hydrocarbons
Biomass burning	5	5	Canada, Africa, and South America, Australia, Southeast Asia	PM 2.5, nitrates, carbon monoxide, sulfur oxide IV, lead, mercury
Vehicles (transport)	5	21	USA, Germany, Russia, Japan	Ultrafine PM, PM 2.5, nitrates, nitrogen oxides, VOCs, ozone
Natural sources	18	2	Countries in Africa and the Middle East	PM 10 air dust

In addition to individual susceptibility factors, vulnerability to outdoor air pollution can be influenced by additional environmental influences such as noise, temperature, proximity to main roads or green areas of the city, and the combined effects of other pollutants and toxins. Thus, in people living near large roads, where the level of noise and pollution from vehicles is high, the tunica intima and tunica media of the carotid arteries are thicker than those living in areas further away from highways [3, 25, 31]. According to consistent results from some studies, the proximity of the roadway to residential areas was associated with an increased risk of acute myocardial infarction [33, 35, 44], sudden cardiac death [47], death from coronary heart disease [47], mortality after stroke [28], and mortality risk after hospitalization with acute heart failure [36]. It is believed that the risk of developing cardiovascular diseases and increased mortality from CVD in people living near major roads are due to vehicle emissions containing ultrafine PM [28, 36].

In addition to ultrafine particulate matter, emissions from road traffic also contain VOCs such as acrolein, benzene, and butadiene, which have been shown to exhibit significant cardiovascular toxicity by themselves [6]. Acute exposure to VOCs, in particular acrolein, can cause dyslipidemia [21], vascular damage [22], endothelial dysfunction [23] and platelet activation [42], whereas chronic exposure accelerates atherogenesis [43], destabilizes atherosclerotic lesions [38], may impair cardioprotective signaling and may cause dilated cardiomyopathy [32, 35]. Hence, VOCs and other gaseous pollutants such as nitric oxide, carbon monoxide, ozone, and sulfates, which account for more than 98% of the mixture we breathe in urban areas, can significantly alter the effects of PM and contribute to CVD in some way, especially in urban areas [7, 14].

Air pollution by particulate matter is also considered as one of the risk factors for comorbid (combined) diseases of the cardiovascular and respiratory systems [12, 18].

The connection between exposure to air pollution and cardiovascular diseases is also supported by data from studies in experimental (preclinical) animal models. Under controlled conditions, increased exposure to ambient PM has been shown to enhance atherogenesis, insulin resistance, and peripheral thrombosis in experimental animals [5, 6]. Experimental and clinical evidence suggests a strong relationship between CVD and air pollution; the underlying mechanisms are still unknown. It is crucial to define physiological and molecular mechanisms to recognize critical factors that control human susceptibility to the toxic action of particulate matter. Understanding will help us learn the effect of the pollutant on CVS health and develop therapeutic and prophylactic measures against this context to reduce CVD risk.

Concerning the mechanisms of the undesirable effects of air pollution on the cardiovascular system health, there are suggestions that PM enhances systemic inflammation and causes imbalances in the autonomic nervous system. According to many researchers, these processes are one of the leading investigation directions in this area. It is believed that particulate matter inhalation can lead to increased inflammation by *spreading* pro-inflammatory or oxidative mediators and cytokines from the respiratory system into the systemic circulation [13, 16, 19]. Inflammation and nervous system disbalances, in turn, potentially contribute to endothelial damage and the development of endothelial dysfunction, increasing the risk of atherosclerosis and thrombosis. Endothelial damage leads to a decrease in the ability to produce

anticoagulant substances and the loss of a protective barrier covering the subendothelial layer. As a result, thrombogenesis occurs, and microthrombi are formed in the affected areas [16, 17]. Also, hypoxia develops due to prolonged exposure to particulate matter on the respiratory system, which enhances inflammatory reactions and oxidative stress, linking exposure to PN to the pathogenesis of CVD [9]. Thus, chronic exposure to PM increases the risk of arterial hypertension, atherosclerosis, and the subsequent formation and complications of CVD.

This opinion is supported by several studies [27, 41]. It has been shown that oxidants formed in the lungs under the influence of PM can accelerate the formation of atherosclerotic lesions [41]. Furthermore, inactivation of the free radical (superoxide) due to the action of the antioxidant enzyme superoxide dismutase in the lungs can prevent endothelial dysfunction and the formation of PM-induced insulin resistance [27]. Remarkably, activation of the receptors in the respiratory system and nerve endings by inhaled particulate matter can lead to heart rate changes, heart rate variability, arrhythmias, and other electrocardiographic changes. Such changes increase the sympathetic tone, which subsequently predisposes to the development of arterial hypertension. These developing hemodynamic and electrophysiological changes may, to some extent, explain the PM-induced increase in the risk of acute cardiovascular events (myocardial infarction, stroke, acute heart failure, etc.) [28, 26, 44, 47] described above.

CONCLUSION

Numerous clinical and experimental evidence presented in this article indicates a close relationship between air pollution and CVD. There is a direct relationship between the degree of air pollution and the risk of CVD development, the risk of complications and deaths from CVD. Concurrently, the specific pathophysiological mechanisms underlying the negative impact of atmospheric air pollution on the pathogenesis of CVD remain poorly understood, which creates the need for further investigation and clarification. Understanding these mechanisms is of fundamental value and significant practical importance, which lies in the possibility of using such information for the development of therapeutic and prophylactic measures to minimize the negative impact of pollutants.

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