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UTICAJ AEROZAGAĐENJA NA EGZACERBACIJE HRONIČNE OPSTRUKTIVNE BOLESTI PLUĆA

Jovan Javorac[1,2], Marija Jevtić[3,4], Dejan Živanović[2], Miroslav Ilić[1,4]

[1] Institut za plućne bolesti Vojvodine, Sremska Kamenica, Republika Srbija
[2] Departman za biomedicinske nauke, Visoka škola strukovnih studija za obrazovanje vaspitača i trenera, Subotica, Republika Srbija
[3] Institut za javno zdravlje Vojvodine, Novi Sad, Republika Srbija
[4] Medicinski fakultet Univerziteta u Novom Sadu, Novi Sad, Srbija

SAŽETAK

Hronična opstruktivna bolest pluća (HOBP) je jedan od vodećih globalnih javnozdravstvenih problema, sa procenom da će do 2030. godine biti treći po učestalosti uzrok smrti. Akutne egzacerbacije HOBP dovode do ubrzanog propadanja plućne funkcije, smanjenja kvaliteta života i povećanog broja hospitalizacija, kao i do smrtnih slučajeva. Najčešći uzrok egzacerbacija su respiratone infekcije, ali se danas sve više ispituje uticaj faktora životne sredine na njihov nastanak. Među njima, aerozagađivači su od najvećeg značaja. Brojne studije sprovedene do sada nedvosmisleno su pokazale da povišene koncentracije suspendovanih čestica (PM), sumpor dioksida (SO_2), azot dioksida (NO_2) i ozona (O_3) u atmosferskom vaduhu imaju najizraženiji negativni efekat na bolesnike sa HOBP, povećavajući učestalost egzacerbacija HOBP kao i posledičnu smrtnost zbog njih. U ispitivanju njihovog uticaja nije dovoljno ispitivati samo efekte pojedinačnih zagađivača vazduha, već i njihove međusobne interakcije, kao i interakcije sa meteorološkim faktorima. U cilju smanjenja opterećenja zdravstvenih sistema ovom bolešću, neophodno je implementirati sve strategije koje će smanjiti učestalost HOBP. To svakako podrazumeva i globalno smanjenje aerozagađenja, što će zahtevati podršku najrazvijenijih svetskih ekonomija, značajno obnavljanje neophodnih resursa i, konačno, korenite društvene promene.

Ključne reči: aerozagađenje, egzacerbacija, hronična opstruktivna bolest pluća, suspendovane čestice, sumpor dioksid, azot dioksid, ozon

Uvod

Hronična opstruktivna bolest pluća (HOBP) je jedan od vodećih globalnih javnozdravstvenih problema, sa prevalencijom od 12% u opštoj populaciji, oko tri miliona smrtnih ishoda godišnje na globalnom nivou (1), i najvišom incidencijom u ekonomski nerazvijenim i zemljama u razvoju (preko 85% svih registrovanih novoobolelih slučajeva) (2). Svetska zdravstvena organizacija (SZO) procenjuje da će 2030. godine HOBP biti treći vodeći uzrok smrti u svetu (3). Hroničan i progresivan tok ovog oboljenja karakterišu periodi remisije sa povremenim pogoršanjima (egzacerbacije) u formi izraženih dispnoičnih tegoba, a koja značajno doprinose bržem propradanju plućne funkcije, smanjenju kvaliteta života, češćoj potrebi za pregledom lekara, češćim hospitalizacijama i, konačno, povećanom umiranju ovih bolesnika (4). Egzacerbacije bolesti su u najvećem broju slučajeva prouzrokovane respiratornim infekcijama virusne ili bakterijske etiologije (50-70% slučajeva), ali se poslednjih godina sve više pažnje posvećuje proučavanju uticaja izloženosti faktorima životne sredine na nastanak akutnih pogoršanja HOBP: zagađivačima vazduha, meteorološkim uslovima, kao i aerogenim štetnostima na radnom mestu.

Prema izveštaju SZO o globalnom opterećenju bolestima iz 2013. godine, zagađenje vazduha je bilo peti po redu značajnosti faktor rizika za nastanak oboljenja, učestvujući sa 6% u izgubljenim godinama zdravog života stanovništva (odnosno DALY-jima, engl. *Disability-Adjusted Life Year*) (5), kao i uzrok oko 4,2 miliona smrtnih ishoda širom sveta (6). HOBP se nalazi na trećem mestu svih uzroka smrti usled zagađenja vazduha (7). Utvrđeno je da porast koncentracija suspendovanih čes-

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THE EFFECT OF AIR POLLUTION ON CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATIONS

Jovan Javorac[1,2], Marija Jevtic[3,4], Dejan Živanovic[2], Miroslav Ilic[1,4]

[1] Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Republic of Serbia
[2] Department of Biomedical Sciences, College of Vocational Studies for the Education of Preschool Teachers and Sports Trainers, Subotica, Republic of Serbia
[3] Institut for the Public Health of Vojvodina, Novi Sad, Republic of Serbia
[4] The Faculty of Medicine, University of Novi Sad, Novi Sad, republic of Serbia

SUMMARY

Chronic obstructive pulmonary disease (COPD) is one of the greatest global public health challenges, emerging as the third leading cause of death by 2030. Acute exacerbations of COPD (AECOPD) contribute to the accelerated deterioration of lung function, reduced quality of life and higher hospitalizations and mortality rates. The cause of exacerbation is usually an infectious agent, but the impact of exposure to environmental factors is being studied more thoroughly. Among them, atmospheric pollutants emerged as the most important ones. Multiple studies showed that elevated concentrations of particulate matter (PM), sulphur dioxide (SO_2), nitric dioxide (NO_2) and ozone (O_3) in the atmosphere, have the most significant negative effect on patients with COPD, increasing hospitalisations and mortality rates due to COPD. While examining their effect on AECOPD, it is important to consider the mutual interactions of different air pollutants, as well as interactions with meteorological factors. In order to decrease the burden of COPD, it is necessary to implement all strategies that will reduce the incidence of COPD, including global reduction of air pollution. That will require the support of the world's most developed economies, a significant renewal of the necessary resources and, finally, radical social change.

Key words: air pollution, chronic obstructive pulmonary disease, exacerbation, particulate matter, sulphur dioxide, nitric dioxide, ozone

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the greatest global public health problems, with the prevalence of 12% in the general population, about three million deathly outcomes per year globally (1), and the highest incidence in economically underdeveloped and developing countries (more than 85% of all registered new cases) (2). The World Health Organization (WHO) estimates that COPD will be the third leading cause of death in the world by 2030 (3). The chronic and progressive course of this disease is characterized by periods of remission with periodical exacerbations in the form of severe dyspnea, which significantly contribute to the accelerated deterioration of lung function, reduced quality of life, need for more frequent medical examinations, more frequent hospitalizations and eventually to higher mortality of these patients (4). Disease exacerbations are in most cases caused by respiratory infections of viral and bacterial etiology (50-70% of cases), but in recent years the impact of exposure to environmental factors on acute COPD exacerbations has been studied more thoroughly: air pollutants, meteorological factors and occupational air pollutants.

According to the World Health Organization's report on the burden of disease from 2013, air pollution was the fifth leading risk factor, with 6% of years of healthy life lost, that is DALYs (Disability-Adjusted Life Years) (5), as well as a cause of about 4.2 million deaths worldwide (6). COPD is the third leading cause of death due to air pollution (7). It was found out that elevated concentrations of particulate matter (PM), sulfur dioxide (SO_2), ground-level ozone (O_3), and nitrogen dioxide (NO_2) in the atmosphere influenced exacerbations of dyspnea and other

ca (PM), sumpor dioksida (SO_2), prizemnog ozona (O_3) i azot dioksida (NO_2) u spoljašnjem vazduhu utiče na pogoršanje dispnoičnih tegoba i ostalih respiratornih simptoma kod bolesnika sa HOBP, sa posledično većim brojem intervencija službi hitne medicinke pomoći, ambulantnih poseta lekaru i broja hospitalizacija, kao i porastom mortaliteta od HOBP (8,9). Ovi problemi mogu da se jave čak i kada su koncentracije aeropolutanata u normativno dozvoljenim vrednostima (10); tj. čak i kada su dostignute preporuke Svetske zdravstvene organizacije (SZO) za održavanje kvaliteta vazduha životne sredine, i dalje postoji povećan zdravstveni rizik od obolevanja, a to se odnosi ne samo na bolesnike koji boluju od HOBP, već i na druge hronične bolesti na koje aeropolutanti mogu imati uticaja. Takođe, postoji mogućnost sinergističkog delovanja među različitim čvrstim i gasovitim zagađivačima vazduha, ali i sa drugim faktorima životne sredine (poput klimatskih faktora), što se mora uzeti obzir u istraživanjima prilikom procene efekta pojedinačnih faktora na akutne egzacerbacije hronične opstruktivne bolesti pluća (AEHOBP) (11).

Cilj ovog preglednog rada je da se analizira značaj aerozagađenja, i to suspendovanih čestica, sumpor dioksida, azot dioksida i ozona, na egzacerbaciju HOBP.

Metode

U cilju analizie značaja aerozagađenja, i to suspendovanih čestica, sumpor dioksida, azot dioksida i ozona na egzacerbaciju HOBP, korišćena je literatura objavljenja na engleskom jeziku tokom poslednjih 25 godina, a koja je dobijena pretraživanjem PUBMED-a korišćenjem sledećih ključnih reči: aerozagađenje, egzacerbacija, hronična opstruktivna bolest pluća, suspendovane čestice, sumpor dioksid, azot dioksid i ozon.

Uticaj suspendovanih čestica na egzacerbaciju HOBP

Suspendovane čestice (PM, engl. *particulate matter*) predstavljaju jedan od najznačajnijih faktora aerozagađenja koji se dovodi u vezu sa egzacerbacijom HOBP. Utvrđeno je da PM, zbog svojih karakterističnih osobina (porekla, veličine, hemijskog sastava), tj. mogućnosti dopiranja do različitih dubina respiratornog sistema, dovode do nadražajnih ili opstruktivnih efekata na nivou bronhija. Na osnovu aerodinamskog dijametra, suspendovane čestice se mogu podeliti na PM_{10} (čestice čiji je dijametar ispod ili jednak 10 μm), grubu frakciju (od 2,5 μm do 9 μm), kao i finu frakciju u koju se ubrajaju $PM_{2,5}$ (veličine od 0,1 μm do 2,5 μm) i ultrafine čestice (ispod 0,1 μm). Najčešće se sistemski prate koncetracije PM_{10} i $PM_{2,5}$ u vazduhu, dok se ultrafine čestice retko rutinski prate. Čestice koje su iznad 2,5 μm u prečniku obično sadrže resuspendovanu prašinu sa puteva, kao i onu nastalu industrijskom aktivnošću, biološke materije kao što su granule polena i fragmenti bakterija, mineralne materije koje se donose vetrom sa poljoprivrednih zemljišta, mineralnih polja, evaporacijom sa površine mora, pepeo i dr. Čestice fine frakcije obično nastaju procesom evaporacije ili kao sekundarni polutanti u atmosferi, nakon čega se dalje procesima kondezacije i koagulacije uvećavaju u prečniku (6). Oko dve trećine PM su antropogenog porekla, nastale sagorevanjem fosilnih goriva, biomase ili emitovanjem amonijaka.

Mehanizimi delovanja PM na ljudski organizam podrazumevaju više različitih efekata: izazivanje inflamacije i oksidativnog stresa u disajnim putevima, hiperreaktibilnost disajnih puteva, smanjenje efekta zaštitnih mehanizama, genotoksičnost i trombogeno delovanje na nivou krvnih sudova. Zdravstvene posledice takvog efekta uključuju: povećan broj hospitalizacija i povećanje stope smrtnosti zbog pogoršanja opstruktivnih oboljenja pluća (HOBP i astma), kao i kardiovaskularnih bolesti (promene arterijskog pritiska, srčane frekvencije, poremećaji ritma, ishemijska bolest srca), šećerne bolesti, ubrzanje procesa ateroskleroze, iniciranje karcinogeze i sl. (6). Eksperimentalne studije su pokazale da PM podstiču nastanak snažnog inflamatornog procesa u disajnim putevima, sa posledičnim pojačanim lučenjem brojnih citokina i slobodnih radikala koji mogu da oštete tkivo (12). Pacijenti sa HOBP imaju deficitarne antioksidativne mehanizme, tako da su veoma prijemčiva kategorija za pogoršanje inflamatornog procesa u zidovima disajnih puteva i akutnu egzacerbaciju HOBP. Epidemiološka istraživanja ukazuju na snažnu korelacionu povezanost čestica PM_{10} i $PM_{2,5}$ sa respiratornim morbiditetom i mortalitetom (13). U studiji *Schikowskog* i saradnika (14), porast koncentracije PM_{10} na 7 $\mu g/m^3$ je bio povezan sa smanjenjem vrednosti forsiranog ekspirijumskog volumena u prvoj sekundi (FEV1) za 5,1% tokom petogodišnjeg praćenja, a stanovanje

respiratory symptoms in patients with COPD, resulting in the increased number of interventions in emergency departments, physician office visits and hospitalizations, as well as in the increase of mortality rates caused by COPD (8,9). These problems may appear even when concentrations of air pollutants are within the limit values (10); that is, even when the WHO air quality guidelines levels are met, the increased health risk for the occurrence of disease still exists, and this does not only relate to COPD patients, but also to other chronic diseases, which could be influenced by air pollutants. Also, synergistic effects of different solid and gas air pollutants are possible, together with other environmental factors (such as factors affecting climate), which has to be taken into consideration in researches during the assessment of effects of individual factors on acute exacerbations of chronic obstructive pulmonary disease (AEHOPD) (11).

The aim of this review article is to analyze the significance of air pollution, that is, the influence of particulate matter, sulfur dioxide, nitrogen dioxide and ozone on COPD exacerbations.

Methods

In order to analyze the significance of air pollution, and the influence of particulate matter, sulfur dioxide, nitrogen dioxide and ozone on COPD exacerbations, we used literature that has been published in the English language during the last 25 years, which we searched with the help of PUBMED using the following words: air pollution, exacerbations, chronic obstructive pulmonary disease, particulate matter, sulfur dioxide, nitrogen dioxide and ozone.

The influence of particulate matter on COPD exacerbations

Particulate matter presents one of the most significant factors of air pollution, which is connected with COPD exacerbations. It was found out that PM, due to its characteristic traits (origin, size, chemical structure), that is, due to their ability to penetrate deep into the respiratory system, leads to irritation or obstructive effects at the level of bronchi. According to the aerodynamic diameter, suspended particles can be divided into PM_{10} (particles with a diameter of 10 μm or less), course particles (from 2.5 μm to 9 μm), as well as fine particles which include $PM_{2.5}$ (from 0.1 μm to 2.5 μm) and ultrafine particles (less than 0.1 μm). Most frequently concentrations of PM_{10} and $PM_{2.5}$ in the air are systematically observed, while ultrafine particles are rarely observed. Particles with a diameter more than 2.5 μm usually contain resuspended particles of road dust, as well as dust which was created due to industrial activities, biological matter such as pollen grains and fragments of bacteria, mineral matter brought by wind from agricultural soils, mineral fields, evaporation from sea surface etc. Particles of fine fraction usually appear in the evaporation process or as secondary pollutants in the atmosphere, and afterwards their diameter increases in the process of condensation and coagulation (6). About two thirds of particles have an anthropogenic origin, and they appear due to combustion of fossil fuels, biomass or ammonia emissions.

The mechanisms of impact of PM on human body include various effects: airway inflammation and oxidative stress, airway hyperresponsiveness, reduced effects of defense mechanisms, genotoxicity and thrombogenic activity in blood vessels. Health consequences of such effects include: increased number of hospitalizations and increase in mortality rates due to exacerbations of obstructive pulmonary diseases (COPD and asthma), as well as cardiovascular diseases (changes in arterial blood pressure, heart frequency, heart arrhythmias, ischemic heart disease), diabetes, accelerated atherosclerosis, initiation of carcinogenesis etc. (6). Experimental studies showed that PM induced the occurrence of strong airway inflammation, resulting in the increased secretion of numerous cytokines and free radicals that can cause tissue damage (12). Patients with COPD have deficient antioxidative mechanisms, and therefore, they are susceptible to the exacerbation of inflammatory process in airway walls and acute exacerbations of COPD. Epidemiological studies point to the strong correlation between PM_{10} and $PM_{2.5}$ and respiratory morbidity and mortality (13). In the study of Schikowski and associates (14), the increase in concentrations of PM_{10} to 7 $\mu g/m^3$ was connected with the value of forced expiratory volume which decreased for 5.1% in one second (FEV1) during the five-year follow-up, while living within 100 meters of the highway was connected with harmful effects on lung function

u dijametru od 100 metara u odnosu na velike saobraćajnice je bilo povezano sa štetnim efektima na plućnu funkciju i predstavljalo faktor rizika za nastanak HOBP kod prethodno zdravih osoba. *Dominici* i saradnici u svojoj studiji (15) ukazuju na skoro udvostručen broj hospitalizacija zbog pogoršanja HOBP za svako povećanje koncentracije $PM_{2,5}$ od 10 μg/m³. Nije samo izloženost PM u spoljašnjem vazduhu faktor rizika za pogoršanje plućne funkcije, već je dokazana i značajna povezanost između prevalencije HOBP i korišćenja biomase u domaćinstvima kao goriva za kuvanje i grejanje u ruralnim predelima Kine, a ovaj efekat je bio najizraženiji kod osoba ženskog pola (16). Pored povećanja morbiditeta, rezultati pojedinih studija govore i u prilog povećanog umiranja pacijenata sa HOBP odmah nakon izlaganja većim koncentracijama PM, a ovaj efekat je uočen i za druge aeropolutante, poput SO_2 i NO_2 (17). U meta-analizi iz 2017. godine, povećanje koncentracije $PM_{2,5}$ od 10 μg/m³ je bilo u vezi sa povećanjem učestalosti ambulantnih pregleda i hospitalizacija zbog HOBP za 2,5% (95% CI: 1,6–3,4%) (18).

Uticaj sumpor dioksida na pogoršanje HOBP

SO_2 može da se nađe u vazduhu emisijom iz prirodnih (npr. vulkanske erupcije, itd.) i antropogenih izvora (npr. izduvni gasovi motornih vozila, korišćenje sulfidnih ruda u termoelektranama, industriji, za grejanje itd.). Neželjena dejstva ostvaruje preko bisulfata koji kao redukciono sredstvo može da smanji količinu glutationa kao oksidacionog sredstva u tkivima. Pored toga, u bronhijalnoj sluznici može dovesti i do nastanka strukturalnih promena u smislu povećanja broja mukoznih ćelija i žlezda, smanjenja mukocilijarnog klirensa i bronhospazma (6). Kao posledica kratkotrajne ekspozicije (kraće od 24 h) povećanim koncentracijama SO_2 u vazduhu, može doći do naglog nastanka bronhospazma i posledičnog smanjenja FEV1, te povećanja endobronhijalnog otpora, rezultirajući konačno pojavom dispnoičnih simptoma (otežano disanje, zviždanje u grudima); ovaj efekat je izraženiji kod astmatičara (19) i bolesnika sa HOBP (20) u odnosu na zdrave pojedince. Dugotrajne ekspozicije (duže od 24h) potencijalno bi mogle da povećavaju učestalost oboljevanja i umiranja od respiratornih i kardiovaskularnih bolesti, ali se ne može sa sigurnošću tvrditi da li je to posledica potenciranja efekta PM ili indirektnog uticaja preko sulfatne kiseline i bisulfata.

Projekat APHEA (engl. *The Air Pollution and Health, a European Approach*) bio je jedan od najvažnijih istraživačkih poduhvata koji se bavio uticajem kratkoročnog izlaganja aerozagađenju na morbiditet i mortalitet u nekoliko evropskih gradova. U jednom delu istraživanja utvrđeno je da je porast koncentracije SO_2 na 50 μg/m³ doveo do porasta dnevne smrtnosti od svih uzroka za 3%, dok su PM_{10} čestice kao uzrok smrti učestvovale sa 2% na dnevnom nivou u isto vreme. Kumulativni efekti produženog izlaganja (dva ili četiri dana) zagađivačima vazduha imalo je slične efekte kao nakon jednodnevnog izlaganja (21). Relativni rizik za hospitalizaciju zbog AEHOBP nakon povećanja koncetracije SO_2 na 50 μg/m³ bio je 1,02 (20). U APHEA 2 projektu, utvrđeno je da porast koncentracije SO_2 za 10 μg/m³ dovodi do porasta učestalosti javljanja službi hitne medicinske pomoći zbog pogoršanja HOBP i astme za 0,6% (22), što sve govori u prilog štetnog delovanja SO_2 na bolesnike sa HOBP.

Uticaj azot dioksida na pogoršanje HOBP

Azot dioksid može nastati nakon što se drugi azotni oksidi iz stratosfere spuste u niže atmosferske slojeve i potom se putem odgovarajućih hemijskih reakcija pretvore u NO_2, zatim kao posledica metaboličkih procesa bakterija, vulkanske aktivnosti, dok su antropogeni izvori češće zastupljeni, i u tom kontekstu NO_2 nastaje kao posledica sagorevanja goriva iz stacionarnih ili mobilnih izvora aerozagađenja (obično se emituje azot monoksid koji u reakciji sa ozonom daje azot dioksid), sagorevanjem duvana, zavarivanjem ili tokom proizvodnje amonijaka (6). U kliničkim studijama, utvrđeno je da izlaganje visokim koncentracijama NO_2 kod ljudi koji imaju HOBP može dovesti do dodatnog smanjenja FVC (forsiranog vitalnog kapaciteta), FEV1 i povećanja endobronhijalnog otpora, sa posledičnim pogoršanjem osnovne bolesti (23).

U više studija dokazano je da kratkotrajno izlaganje O_3, NO_2 i SO_2 povećava broj hospitalizacija zbog HOBP, a među ovim gasovitim aeropolutantima, NO_2 je bio najjači prediktor hospitalizacija (24). Razlog za to je možda u činjenici da ovaj gas nije preterano rastvorljiv, pa dospeva do najsitnijih bronhijalnih puteva gde izaziva štetne efekte. U prethodnoj pomenutoj meta-analizi iz 2017.

and it presented a risk factor for the occurrence of COPD in previously healthy persons. Dominici and associates in their study (15) pointed to the fact that the number of hospitalizations due to COPD exacerbations doubled for each increase of 10 μg/m³ in the concentrations $PM_{2.5}$. The exposure to PM in the atmosphere is not the only risk factor for the exacerbation of pulmonary function. However, the significant correlation between the prevalence of COPD and the use of biomass for cooking and heating in households in the rural regions of China was proved, and this effect was more pronounced in women (16). In addition to the increase in morbidity, results of several studies point to the increased mortality among patients with COPD immediately after the exposure to increased concentrations of PM, and this effect was noticed in other air pollutants, such as SO_2 and NO_2 (17). In the meta-analysis form 2017, the increase of 10μg/m³ in the concentrations of $PM_{2.5}$ was connected with the increase in the number of infirmary examinations and hospitalizations due to COPB for 2.5% (95% CI: 1.6-3.4%) (18).

The impact of sulfur dioxide on the COPD exacerbation

SO_2 can be found in the air due to emissions from natural sources (for example, volcanic eruptions) and anthropogenic sources (vehicle exhaust gases, use of sulfide ores in thermal power stations, industry, heating etc.). Side effects are caused by bisulfates, which as reducing agents can reduce the amount of glutathione as an oxidizing agent in tissues. In addition to this, structural changes can appear in bronchial mucosa, such as the increase in the number of mucous cells and glands, a decrease in mucociliary clearance and bronchospasm (6). Short exposure (less than 24 h) to the elevated concentrations of SO_2 in the air can cause sudden bronchospasm and consequential FEV1, as well as the increased endobronchial resistance, resulting in dyspnoeic symptoms (heavy breathing, wheezing); this effect is more pronounced in patients with asthma (19) and patients with COPD (20) in comparison to healthy individuals. Long-term exposure (longer than 24 h) could possibly increase the frequency of disease occurrence and mortality caused by respiratory and cardiovascular diseases, but it cannot be stated with certainty whether this is the consequence of stressing the effects of PM or indirect impact through the sulfuric acid or bisulfates.

The Air Pollution and Health, a European Approach (APHEA) project was one of the most important research undertakings, which dealt with the influence of short-term exposure to air pollution on morbidity and mortality in several European cities. In one part of the research it was found out that the increase of 50μg/m³ in the concentrations of SO_2 led to the increase in daily mortality due to all causes for 3%, while at the same time PM10 particles as a cause of death participated with 2% on a daily basis. Cumulative effects of prolonged exposure (two or four days) to air pollutants had similar effects as after exposure that lasted one day (21). A relative risk for the hospitalization due to AECOPD after the increase of 50μg/m³ in the concentrations of SO_2 was 1.02 (20). In the APHEA project, it was found out that the increase of SOs concentrations for 10μg/m³ led to the increase in the number of visits to emergency departments due to the exacerbations of COPD and asthma for 6% (22), which confirms the harmful effects of SO_2 on patients with COPD.

The impact of nitrogen dioxide on COPD exacerbation

Nitrogen dioxide can appear after other nitrogen oxides descend from the stratosphere to lower layers of atmosphere and then turn to NO_2 by means of certain chemical reactions, then as a consequence of metabolic processes of bacteria, volcanic activity, whereas anthropogenic sources are more common, and in that context NO_2 appears as a consequence of fossil fuels combustion from the stationary or mobile sources of air pollution (usually emissions of nitrogen monoxide, which in reaction with ozone gives nitrogen dioxide), tobacco smoke, welding or ammonium production (6). In clinical studies, it was found out that exposure to high concentrations of NO_2 in people who have COPD can lead to additional FVC (forced vital capacity), FEV1 and increase of endobronchial resistance, with the consequential exacerbation of main disease (23).

It was proved in several studies that short-term exposure to O_3, NO_2 and SO_2 increases the number of hospitalizations due to COPD, and among these gaseous air pollutants, NO_2 was the strongest predictor of hospitalizations (24).

godine (18), povećanje koncentracije NO_2 za 10 µg/m³ bilo je povezano sa povećanjem ambulantnih poseta lekaru i hospitalizacija zbog HOBP za 4,2% (95%CI: 2,5–6,0%). Relativni rizik za hospitalizaciju zbog AEHOBP nakon povećanja koncetracije NO_2 za 50 µg/m³ u APHEA projektu bio je 1,02 (20).

Uticaj ozona na pogoršanje HOBP

Ozon je sekundarni zagađivač vazduha, što znači da se ne emituje direktno iz izvora aerozagađenja. Umesto toga, proizvodi se kada se ugljen monoksid (CO), metan ili druga isparljiva organska jedinjenja (VOCs) oksidišu u prisustvu azotnih oksida (NOk) i sunčeve svetlosti. Osnovni mehanizam negativnog delovanja na respiratorni sistem je oksidacija odgovarajućih komponenti sekreta nad respiratornim epitelom, pri čemu nastaju slobodni radikali koji doprinose pojačanju inflamatornog procesa i oštećenju epitelnih ćelija. Pored toga, ozon utiče na smanjenje mukocilijarnog klirensa, povećava reaktibilnost bronha, a dugotrajnom ekspozicijom nastaju strukturalne promene u smislu hiperplazije mukoznih ćelija i žlezda, zadebljanja zida bronha i alveolarne fibroze (6). Ovakvi efekti mogu da ugroze respiratornu funkciju, izazivajući opstruktivne promene u respiratornom traktu, naročito kod osoba koje već boluju od astme i/ili alergijskog rinitisa (25), ali je ovakav efekat uočen i kod bolesnika sa HOBP.

U studiji *Stieba* i saradnika utvrđeno je da porast koncentracije O_3 za 18,4 µg/m³ dovodi do povećanja ukupnog broja pregleda pacijenata usled pogoršanja astme (3,2%) i HOBP (3,7%) (26). U studiji koju je sproveo *Schwartz* (27) otkriveno je da je O_3 povezan sa povećanim rizikom od hospitalizacije zbog AEHOBP. Takođe, studija koja je sprovedena u iranskoj prestonici Teheranu (28), pokazala je da povećanje koncentracije O_3 u vazduhu za 10 µg/m³ istovremeno povećava i rizik od AEHOBP za 0,86% (95% CI: 0,44–1,3%), a 93% od ukupnog broja hospitalizacija je moglo biti pripisano danima u kojima koncentracija O_3 nije prešla 110 µg/m³.

Zaključak

Dosadašnja istaživanja nedvosmisleno su dokazala da povećane koncetracije PM, SO_2, NO_2 i O_3 dovode do pogoršanja simptoma kod bolesnika sa HOBP. Iako neke studije pokazuju da se u poslednje vreme beleži smanjenje koncentracija O_3 i NO_2 na globalnom nivou kao posledica primene efikasnih strategija za smanjenje zagađenja vazduha, PM, O_3, NO_2 i SO_2 još uvek imaju izražen uticaj na pojavu AEHOPB. Budući da je korelacija pomenutih aeropolutanata sa geografskim, demografskim i klimatskim karakteristikama različitih regiona u svetu još uvek nedovoljno proučena, jasno je da postoji objektivna potreba za daljim istraživanjima u ovoj oblasti.

Svaka procena kvaliteta vazduha životne sredine i utvrđivanje povezanosti sa obolevanjem stanovništva, odnosno procena uticaja faktora životne sredine na zdravlje stanovništva, od neprocenjive je važnosti za unapređenje politike unapređenja zdravlja stanovništva i upravljanja kvalitetom vazduha životne sredine. Globalna eliminacija zagađenja vazduha će zahtevati podršku najrazvijenijih svetskih ekonomija, značajno obnavljanje neophodnih resursa međunarodne zajednice i, konačno, korenite društvene promene. Da bi se ovi ciljevi ostvarili, neophodno je da sve države u svetu postepeno pređu na korišćenje obnovljivih izvora energije koji ne zagađuju životnu sredinu, smanje emisiju štetnih gasova u saobraćaju i redizajniraju industrijske procese, kako bi se smanjilo stvaranje otpadnih materija i pomerilo sa ekonomskih modela razvoja zasnovanih na masovnom utrošku prirodnih resursa ka održivom ekonomskom modelu razoja.

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A reason for that may be in the fact that this gas is not very soluble, and therefore, it reaches the tiniest bronchial ways, where it causes harmful effects. In the previously mentioned meta-analysis from 2017 (18), the increase in NO_2 concentrations for 10 μg/m³ was connected with the increase in physician office visits and hospitalizations due to COPD for 4.2% (95% CI: 2.5-6.0%). A relative risk for the hospitalization due to AECOPD after the increase in NO_2 concentrations for 50 μg/m³ was 1.02 in the APHEA project (20).

The impact of ozone on COPD exacerbation

Ozone is the secondary air pollutant, which means that it is not emitted directly from the source of air pollution. Instead of that, it is produced when carbon monoxide (CO), methane or other volatile organic compound (VOCs) react in the presence of nitrogen oxides and sunlight. The basic mechanism of negative influence on the respiratory system is the oxidation of certain components of secretion of the respiratory epithelium, when free radicals appear and contribute to the intensification of inflammatory process and epithelial cells damage. In addition to this, ozone influences the decrease of mucociliary clearance, the increase in bronchial reactivity, while long-term exposure causes structural changes, such as the hyperplasia of mucous cells and glands, bronchial wall thickening and pulmonary alveolar fibrosis (6). Such effects can endanger the respiratory function, thus causing obstructive changes in the respiratory tract, especially in persons already affected by asthma and/or allergic rhinitis (25). However, this effect was noticed in patients with COPD as well.

In the study of Stieb and associates, it was found out that the increase in O_3 concentrations for 18.4 μg/m³ led to the increase in the total number of examinations due to exacerbations of asthma (3.2%) and COPD (3.7%) (26). In the study conducted by Schwartz (27), it was found out that O3 was connected with the increased risk of hospitalization due to AECOPD. Also, the study, which was conducted in the Iranian capital city, Teheran (28), showed that the increase in O_3 concentrations in the air for 10 μg/m³ simultaneously increased the risk of AECOPD for 0.86% (95% CI: 0.44-1.3%), while 93% of the total number of hospitalizations could be attributed to days when O_3 concentration did not exceed 110 μg/m³.

Conclusion

Previous research results have unambiguously proved that increased concentrations of PM, SO_2, NO_2 and O_3 lead to the exacerbations of symptoms in patients with COPD. Although some studies show that in recent years, the decrease in O_3 and NO_2 concentrations has been registered globally as a consequence of efficient strategies applied in order to reduce air pollution, PM, O_3, NO_2, and SO_2 still have a pronounced impact on the AECOPD occurrence. Having in mind the fact that the correlation between the above mentioned air pollutants and geographical, demographic and climate characteristics of different world regions has not been studied enough, it is clear that there is the objective need for further research in this field.

Each estimate of ambient air quality and determination of connectedness with disease occurrence, that is, the assessment of influence of environmental factors on population health is of utmost importance for the promotion of health policy and management of ambient air quality. Global elimination of air pollution will demand the support of the most developed world economies, significant recovery of necessary resources of the international community and finally, radical social changes. To achieve these goals, it is necessary that all countries in the world gradually switch to renewable energy sources, which do not pollute the environment, decrease the emission of traffic-related harmful gases and redesign industrial processes, in order to decrease the production of waste and shift from economic models of development based on mass consumption of natural resources to sustainable economic model of development.

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Autor za korespondenciju: Jovan Javorac, Institut za plućne bolesti Vojvodine, Put dr Goldmana 4, 21204, Sremska Kamenica, Srbija; email: jovanjavorac@vsovsu.rs

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Corresponding author: Jovan Javorac, Institute for Pulmonary Diseases of Vojvodina, Put dr Goldmana 4, 21204, Sremska Kamenica, Serbia; e-mail: jovanjavorac@vsovsu.rs