



The response ranges of pulmonary function and the impact criteria of weather and industrial influence on patients with asthma living in Vladivostok

Lyudmila V. Veremchuk¹ · Elena E. Mineeva¹ · Tatyana I. Vitkina¹ · Elena A. Grigorieva² · Tatyana A. Gvozdenko¹ · Kirill S. Golokhvast^{1,3}

Received: 14 February 2019 / Accepted: 10 February 2020
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Abstract

Purpose To determine the response of pulmonary function (PF) to the influence of environmental factors in patients with different levels of asthma control.

Materials and methods Patients with controlled (136 people) and uncontrolled (96 people) asthma living in the conditions of monsoon climate and technogenic pollution in Vladivostok were examined. Discriminant analysis that provides the basis for dividing initial data into classes, as according to standards and expert estimates, was used to calculate ranges of PF response in asthma patients. The selection of discriminant functions with the highest values of constant and coefficient made it possible to identify the optimal quantitative ranges.

Results Analysis of the discriminant value of Wilks' lambda (α) has shown that the intensity of PF response to climatic and technogenic factors varies depending on level of disease control (controlled asthma – $\alpha = 0.67–0.79$, uncontrolled asthma – $\alpha = 0.05–0.44$). The criteria and ranges of PF response also differ depending on level of disease control. In controlled asthma, PF response reflects an adaptive-compensatory dependence. The reaction to the environmental factors is rather weak; therefore, it could be detected by only more sensitive examination method (body plethysmography). In uncontrolled asthma, the response to the influence of environment quality is active and could be clearly identified by spirometry.

Conclusions The climatic and technogenic environment of Vladivostok causes strong pathogenic impact on patients with uncontrolled asthma. The effects of dust fraction $0–1\ \mu\text{m}$, deeply penetrating into respiratory organs, and day-to-day variability of wind speed, which induces weather sensitivity, are particularly adverse.

Keywords Weather · Industrial factors · Respiratory system · Pulmonary function · Asthma

Introduction

The wide spread of asthma in large cities became the reason for the increased attention of researchers to this disease [1–4].

✉ Tatyana I. Vitkina
tash30@mail.ru

¹ Vladivostok Branch of Federal State Budgetary Science Institution, Far Eastern Scientific Center of Physiology and Pathology of Respiration, Institute of Medical Climatology and Rehabilitative Treatment, Vladivostok, Russian Federation

² Institute for Complex Analysis of Regional Problems Far Eastern Branch of Russian Academy of Sciences, Birobidzhan, Russian Federation

³ Far Eastern Federal University, Vladivostok, Russian Federation

Asthma is a heterogeneous disease characterized by chronic inflammation of the airways. Based on clinical symptoms against the background of the basic therapy, asthma is classified as controlled, partially controlled and uncontrolled. Long-term goals in asthma treatment are to achieve good symptom control and minimize the risk of exacerbations [2]. According to modern views, the nature and course of asthma largely depend on the level of technogenic air pollution and climatic features [1, 3–8]. The relationship between meteorological factors and the prevalence of asthma has been convincingly demonstrated in studies [9, 10]. The impact of climate on the respiratory system of patients with asthma activates nonspecific mechanisms of disease manifestation. The industrial pollution aggravates the course of disease and can be a source of specific allergens [11–17]. Suspended particulate matter (SPM), being the most common air pollutant, causes an

increase in the morbidity and mortality of patients with asthma, as well as the worsening of disease symptoms and more frequent exacerbations [18, 19]. It is well documented that air pollution factors interact with daily variations in meteorological factors, such as ambient air temperature, relative humidity, barometric pressure, wind speed and precipitation, when related to asthma attack rate [3, 20–29]. The respiratory system is the system most sensitive to the air quality. Changes in its functioning lead to a shift in body homeostasis. The response of respiratory system to external influences may vary depending on the level of asthma control [30–33]. Therefore, the determination of criteria for external exposure and tolerance of pulmonary function (PF) is the one of the most important hygienic tasks.

The monsoon oceanic climate of Vladivostok has seasonal and daily features of atmospheric circulation and humidity, which significantly impact not only the pollution levels in city atmosphere, but also the physical well-being of people [7, 31, 32]. The influence of weather and industrial parameters on the asthma course has been established [4, 7, 13, 15, 30, 31, 34, 35], but the strength, direction and regional characteristics of the impact of environmental factors are still unclear. Therefore, it is important to study the exposure criteria of trigger climate and industrial factors in urbanized areas that cause changes in PF during asthma exacerbation. This will make it possible to regulate the treatment and prevention processes at different levels of asthma control.

The aim of the study is to determine the response of pulmonary function (PF) to the influence of environmental factors in patients with different levels of asthma control.

Materials and methods

The study involved patients with asthma of various control levels, living under the conditions of monsoon climate and high technogenic air pollution associated with transport emissions (Vladivostok city, Russian Federation).

Examination of asthma patients

Informed consent was obtained from all individual participants included in the study. All procedures in studies involving human participants complied with the ethical standards of the Ethics Committee, Vladivostok Branch of Federal State Budgetary Science Institution “Far Eastern Scientific Center of Physiology and Pathology of Respiration” – Institute of Medical Climatology and Rehabilitative Treatment (identification code of the protocol of Ethics Committee: 10/12–11, approval date: December 07, 2011), and with the Declaration of Helsinki.

The study included 232 subjects with controlled (136 patients) and uncontrolled (96 patients) asthma living in

Vladivostok under the conditions of the monsoon climate and the man-made pollution during the winter period. Patients were examined at the cold season with temperatures below zero degrees Celsius from November to March for years 2012–2017.

Asthma was diagnosed in accordance with the guidelines of the Global Strategy for Asthma Management and Prevention [2]. The CQ-5 test (Asthma Control Questionnaire) was used to assess asthma control. Patients with a score above 1.5 were considered as patients with uncontrolled asthma, and patients with a score from 0 to 0.75 were considered as patients with controlled asthma. Exclusion criteria were: partial control of asthma, chronic obstructive pulmonary disease, occupational respiratory diseases, cardiovascular diseases (coronary heart disease, hypertension) and their complications, diabetes mellitus, and acute and chronic respiratory diseases during the stage of decompensation.

PF of asthma patients was assessed in standard conditions using the “Master Screen Body” equipment (Care Fusion, Germany). The flow and volume indicators were registered during the forced expiratory maneuver and body plethysmography. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume after 1 s (FEV1), FEV1/FVC, peak expiratory flow (PEF) were evaluated by spirometry methods. Static lung volumes (functional residual capacity (FRC_{plet}), total lung capacity (TLC), residual volume (RV), residual volume/ total lung capacity (RV/TLC)) and bronchial resistance (total airway resistance (R_{tot}), inspiratory resistance (R_{in}) and expiratory resistance (R_{ex})) were analyzed by body plethysmography methods. The study of the reversibility of air-flow obstruction was conducted using the salbutamol test (400 µg).

Study of air pollution

The estimation of air pollution in Vladivostok (SPMs, mg/m³) was carried out according to the monitoring data from six stationary observation posts of Primorsky Office of “The Federal Service for Hydrometeorology and Environmental Monitoring” (PO FSHEM) over the cold season in 2012–2017. The data of one-time sampling in different districts of the city that were provided by “The Center of Hygiene and Epidemiology in the Primorsky Krai” were also used [36, 37]. The level of air pollution by dust aerosols in the city was detected by analyzing snow samples over the winter period (for years 2012–2017) [38, 39]. The samples were collected from the upper layer (5–10 cm) of the fresh snow from an area of 1 m² [40]. The size distribution of dust particles was determined by assessing SPMs with Hitachi S-3400 N microscope (Japan) and Ultra Dry energy-dispersive spectrometer (Thermo Scientific, USA) [40–42]. The particle size ranges that characterized the pathophysiological mechanism of toxic action on human respiratory system (0–1, 1–10, 10–50, 50–

100, 100–400, 400–700, >700 μm ; %) were used, taking into account the concentration of toxic metals absorbed on these particles (Pb, Cr, Mn, Fe, Co, Ni, Cu, Zn; $\mu\text{m l}^{-1}$) (15 parameters).

Since Vladivostok is one of Russia's leading cities in terms of the number of cars per capita, motor vehicle emissions are one of the major contributors to the air pollution in city. Therefore, the authors used the indirect indicator (the density of highways) calculated as a ratio of the road area to the total area of district (1 km^2) where patient lives [6, 41, 42].

Weather data

Weather monitoring data (provided by PO FSHEM) for Vladivostok were studied for the periods when the patients were examined. 7 main meteorological parameters (air temperature, air humidity and air pressure, wind direction, wind speed, amount of precipitation, atmospheric phenomena) were considered. The variability index (gradient readings) of meteorological parameters over 1 and 2 days before patient examination was used to assess PF response (14 parameters) [20].

Statistical analysis

The response ranges of PF and the criteria of environment impact in patients with controlled and uncontrolled asthma were determined using discriminant analysis (STATISTICA 8) [43]. The environmental factors and PF parameters were divided into classes. Since hygienic standards for environmental factors are developed mainly for healthy population, we used average values of environmental factors (with normal distribution of values) when dividing the parameters into classes.

The values of environmental factors were divided into 3 classes and coded as (< $x-m$ – code 1; $x \pm m$ – code 2; $>x+m$ code 3). The PF parameters were coded according to medical standards, where the values within the normal range were coded as “1”, the values below the normal range were coded as “2”, and the values above the normal range were coded as “3”. The algorithm for determining the ranges and criteria was carried out in two stages. At the first stage, the response of each encoded PF parameter to the effect of the quantitative values of the factors of climatic-technogenic environment was determined. At this stage, the discriminant analysis in the calculations was equivalent to a multiple regression case (the class code of PF parameter was the dependent variable). The degree of discriminant relationship between PF parameters divided into classes and quantitative values of environmental factors (response of PF on environmental impact) was evaluated by the Wilks' lambda (α). The α value approaching zero ($p < 0.05$) indicated an increase in the discriminant dependence (in the intensity of PF response). As the result, trigger factors, which have α values with high statistical significance,

were selected. The use of quantitative characteristics of environmental factors increased the sensitivity of method when choosing trigger factors. Taking into consideration the hypothetical possibility of “feedback”, when the dependent variable may be an encoded class of the environmental parameter, similar calculation procedure was carried out for the selected trigger environmental factors.

At the second stage, pairwise discriminant analysis was performed to compare statistically highly significant α values of PF parameters and environmental factors (trigger factors). As the result, we calculated the optimal classification functions for each pair of “environmental factor-PF parameter”. On the basis of the obtained regression formulas, we selected classes that had the highest values of the constant (a) and the coefficient (b), by which quantitative ranges and criteria were determined. Each class had a given quantitative characteristic, which were taken as criteria and ranges.

Results and discussion

The discriminant analysis in the groups of patients with controlled and uncontrolled asthma made it possible to identify the environmental trigger factors to which PF parameters responded. As the result of calculations carried out at the first and second stages, we have identified 8 trigger environmental factors (4 air pollution factors and 4 meteorological parameters) that caused response of 7 PF parameters (R tot, FRCple, TLC, RV, FEV1, FEV1/FVC, PEF) in the group of patients with controlled asthma (Table 1).

In the group of patients with uncontrolled asthma we have established 7 trigger environmental factors (5 air pollution factors and 2 meteorological parameters) that caused reaction of 3 PF parameters (VC, FEV1/FVC, PEF) (Table 2).

It has been shown that patients with controlled asthma have higher α values that reflects lower dependence of PF on the environmental characteristics compared to the group of patients with uncontrolled asthma. Low dependence of controlled asthma on environmental factors suggests the formation of adaptive-compensatory mechanisms. High statistical significance ($p = 0.0001$ – 0.003) convincingly confirms the obtained results. In patients with uncontrolled asthma, PF response strongly depended on the quality of environment ($\alpha = 0.05$ – 0.44 ; $p = 0.0008$ – 0.04) (Table 2). The patients with uncontrolled asthma react most negatively to daily changes in wind speed ($\alpha = 0.05$; $p = 0.04$), which indicates the formation of meteorological sensitivity in patients with uncontrolled asthma living in Vladivostok.

When considering the structure of the external impact, represented by the nature and number of trigger factors, it has been found that the parameters of technogenic pollution have the prevailing pathogenic impact on PF (controlled asthma: 4 factors, uncontrolled asthma: 5 factors). Dust particles with

Table 1 The response ranges of PF and the criteria of impact of weather and man-made factors in patients with controlled asthma in Vladivostok

Environmental factors	Discriminant function (α/p)	Criteria of environmental factors	Response ranges of PF	PF parameters
Air pollution				
Density of highways, % kPa*s l ⁻¹	0.78/0.003	>50	>0.35	R tot,
Dust fractions 1–10 µm, % kPa*s l ⁻¹	0.78/0.002	>20	>0.35	R tot,
Level of Co in the air, µg/l % predicted	0.79/0.003	>0.5	70–81	FEV1,
Level of SPM in the air, mg/m ³	0.73/0.0008	>1.0	60–70	FEV1/FVC, %
Weather				
Air pressure change, mmHg (a day before the examination)	0.68/0.0001	>10	120–135	FRCplet, % predicted
Air pressure change, mmHg (2 days before the examination)	0.67/0.0001	>8	125–130	FRCplet, % predicted
Air pressure change, mmHg (a day before the examination)	0.78/0.003	>9	135–140	RV, % predicted
Change of precipitation, mm (a day before the examination)	0.75/0.0008	>3.7	>125 < 75	TLC, % predicted
Air humidity change, % (2 days before the examination)	0.77/0.002	>20	60–65	PEF, % predicted
Air pressure change, mmHg (a day before the examination)	0.72/0.0003	>9	<65	PEF, % predicted

diameter of 0–1 µm ($\alpha = 0.17$; $p = 0.0008$), which are able to penetrate deeply into the respiratory organs, are the most dangerous. Among toxic metals, Co has an impact on PF in controlled asthma. An addition to Co, Zn also becomes the trigger factor in uncontrolled asthma. The number of trigger climatic parameters in asthma is less than the number of technogenic ones (controlled asthma: 3 factors, uncontrolled asthma: 2 factors) (Tables 1, 2). However, it has been established that the parameter “change in wind speed over 1 day before the examination” showed the highest pathogenicity ($\alpha = 0.05$; $p = 0.04$). It can be explained by the peculiarities of the

monsoon climate associated with high weather variability, the indicator of which is the wind speed. The obtained result indicates that the climate of Vladivostok is extremely unfavorable for patients with an uncontrolled asthma, especially in the cold season.

The results have demonstrated the difference in PF response to the effect of environmental factors depending on the level of disease control. In controlled asthma, the air pollution factors have a less pronounced effect on PF parameters that characterize bronchial patency ($\alpha = 0.73$ – 0.79) (Table 1). The air pollution by suspended particles has the greatest

Table 2 The response ranges of PF and the criteria of impact of weather and man-made factors in patients with uncontrolled asthma in Vladivostok

Environmental factors	Discriminant function (α/p)	Criteria of environmental factors	Response ranges of PF	PF parameters
Air pollution				
Level of SPM in the air, mg/m ³	0.27/0.003	>0.15	50–70	VC, % predicted
Level of Co in the air, µg/l	0.42/0.02	>0.001	70–80	VC, % predicted
Dust fractions 1–10 µm, %	0.44/0.03	>15	35–70	FEV1/FVC, %
Dust fraction 0–1 µm, %	0.17/0.0008	>12	30–55	PEF, % predicted
Level of Zn in the air, µg/l	0.37/0.01	>0.01	30–60	PEF, % predicted
Weather				
Air humidity change, % (a day before the examination)	0.31/0.009	>10	70–80	VC, % predicted
Wind speed change, m/s (a day before the examination)	0.05/0.04	>4	30–50	FEV1/FVC, %

influence on one of the main parameters characterizing bronchial obstruction – FEV1/FVC ($\alpha = 0.73$; $p = 0.0008$).

In uncontrolled asthma, environmental pollution factors affect not only PF parameters that characterize bronchial obstruction – FEV1/FVC and PEF ($\alpha = 0.17$ – 0.44), but also VC ($\alpha = 0.27$ – 0.42), which can also be decreased during severe obstruction in this form of asthma (Table 2). Dust fractions of 0–1 μm have the greatest influence on bronchial patency (PEF) ($\alpha = 0.17$; $p = 0.0008$), while air pollution by SPM contribute to the change in VC ($\alpha = 0.27$; $p = 0.003$).

In controlled asthma, PF response reflects only adaptive-compensatory dependence. The reaction to the impact of the qualitative characteristics of the environment is too weak ($\alpha = 0.67$ – 0.79), therefore it could be estimated by more sensitive method (body plethysmography). The response to the influence of environment quality in patients with uncontrolled asthma is more pronounced, active ($\alpha = 0.05$ – 0.44) and could be clearly identified by spirometry (Table 2).

Vladivostok is the largest city in the Russian Far East. The main source of air pollution in the city is automobile transport. According to statistics, Vladivostok holds one of the leading places in Russia in terms of the number of cars. However, the ecological situation in city rarely reaches critical level, especially in winter, when increased wind speed is typical. This pattern was also noted in the studies conducted in Vladivostok by V.G. Svinukhov (2000) and P.A. Abbasov (2007), which showed the dependence of the level of atmosphere self-cleaning from multiple climatic features associated with the monsoon climate of city [44, 45].

Environmental pollution exposure significantly increases the risk of respiratory diseases, particularly asthma. Both adult and young patients, smokers or non-smokers, are prone to acute asthma attacks as a result of greater exposure to air pollution [46]. As one of the most pathogenic components of the atmosphere, even in conditions of relatively low pollution, SPM impairs the function of respiratory system in children and adults [5, 35, 47, 48]. In our study, the structuring of trigger factors has shown the predominance of pathogenic effect of anthropogenic environment on PF in patients with controlled and uncontrolled asthma.

The features of monsoon climate (seasonal atmospheric circulation, day-to-day change in weather events, high humidity, etc.) cause increased physiological strain on human respiratory function, thus inducing weather sensitivity [16, 38, 49]. The increased meteosensitivity is typical for patients with asthma. In 30–50% of cases, climatic factors are the cause of exacerbation for this disease. Meteorotropic reactions are characterized by the development of shortness of breath. The study of pulmonary ventilation during meteorotropic manifestations has showed the decrease in vital lung capacity and other PF parameters of patients. Some weather conditions, including extremely high and low temperatures, changes in atmospheric pressure and humidity, as well as wind, can initiate asthma attacks [49–51]. Our findings are in

good agreement with results by Abe et al. for Japan: they demonstrate that cold temperature in monsoon climate is related to an increased risk of significant exacerbation of asthma in adults [3].

Asthma is characterized by airway hyperresponsiveness, airway obstruction, chronic inflammation, and airway remodeling. Pathological meteosensitivity in asthma is accompanied by additional dysfunction of multiple regulatory systems, including those that regulate the inflammatory process. The increase in the cohort of patients who do not achieve disease control despite treatment can be explained, at least in part, by different responses to climatic factors and air pollution [46]. It is known that the patients with respiratory diseases, compared to healthy people, have the reduced capabilities of body adaptive mechanisms that underlie the development of disadaptation reactions to the weather pathogens. These facts suggest that it is important to determine the threshold criteria which may indicate increases in weather sensitivity. Literature review has shown that air temperature has a significant impact on the course of asthma [13, 15, 34, 52, 53]. However, our study has revealed an increase in the activity of PF response to changes in atmospheric pressure, air humidity, and wind speed in both groups of asthma patients. It indicates regional features of the influence of the Far Eastern monsoon climate.

There are practically no comparable studies of the influence of climatic and technogenic factors on lung function in patients with asthma of different control levels. In our study, it was shown for the first time that the intensity of PF response to climatic and technogenic factors changes depending on the level of disease control (controlled asthma – $\alpha = 0.67$ – 0.79 , uncontrolled asthma – $\alpha = 0.05$ – 0.44). The criteria and ranges of PF response also differ depending on the disease control. The activity of PF response to the effect of environmental quality was studied on the basis of the analysis of the number of responded parameters, which were diagnosed by different methods (spirometry and body plethysmography), and the method of body plethysmography was considered as a more sensitive one. The assessment of PF response to external exposure in patients with controlled asthma showed high activity (6 of 10 parameters) of R tot, FRC, RV, TLC (body plethysmography) and slightly reduced activity of the indicators detected by spirometry (FEV1, FEV1/FVC, PEF) (4 of 10 parameters) (Table 1). In uncontrolled asthma, all 7 parameters of PF reaction were identified by the traditional examination method, spirometry (Table 2). The obtained results can be explained by different sensitivity of the diagnostic methods.

The calculation of the criteria and ranges of PF response in different levels of disease control made it possible to establish indicators for characterizing the quality of the environment. When comparing effects of the same environmental factors (“Level of SPM in the air”, “Level of Co in the air”, “Dust fractions 1–10 μm ”) in groups with different levels of disease control, the decrease in the threshold of negative effect of these factors on PF has been established (Tables 1, 2).

Based on the detailed analysis of PF reaction to the qualitative characteristics of environmental factors, the highest pathogenic dependence was identified for patients with uncontrolled asthma. The effect of dust fractions of 0–1 μm ($\alpha = 0.17$; $p = 0.0008$) deeply penetrating into respiratory organs is particularly unfavorable when their content in the air is $>12\%$. Exposure to micro-sized fractions of SPM can alter the normal immune response of lungs, disrupt bronchial mucosa, cause death of epithelial cells and lung fibroblasts, and inhibit intercellular communication between these cells [54, 55].

The effect of Co ($> 0.001 \mu\text{g/L}$) and Zn ($> 0.01 \mu\text{g/l}$) contained in the air on PF parameters (VC and PEF) is quite specific (Table 2). The number of studies suggests that Zn is associated with increased mortality [56]. Burnett et al. have shown that fine Co fractions also significantly correlated with mortality [57]. In addition, Co may act as an allergen. The source of Zn in the city with high vehicle-to-population ratio may be presented by road dust containing tire wear products. The main sources of Co in Vladivostok are motor vehicles and heating stations. Against the background of the negative influence of pollution, PF is especially vulnerable to the influence of “Change in wind speed over a day before the examination” ($\alpha = 0.05$; $p = 0.04$) in the group of patients with uncontrolled asthma, and the lower limit of the gradient of wind speed change is quite low for Vladivostok ($> 4 \text{ m/s}$). It supports the hypothesis of high weather sensitivity of patients with uncontrolled asthma living in the monsoon climate.

The study had certain advantages and disadvantages. Firstly, the strength of study is the use of pulmonary function as an objective measure of respiratory health. Secondly, the level of asthma control was taken into account for the first time. As the study has shown, the structure of the influence of environmental factors and the response ranges change depending on the level of disease control.

Besides that, the study had several limitations. Firstly, we investigated only the influence of outdoor exposure, not indoor factors. The second limitation is that the variability of various PF parameters depends on age, so these parameters should be studied separately for pediatric and elderly patients.

Conclusions

The discriminant analysis made it possible to identify and establish the intensity and criteria for the impact of trigger factors on PF in asthma patients living in climatic and industrial conditions of Vladivostok. Patients with different level of asthma control react to weather and man-made environment with varying intensity. PF response to the effect of qualitative characteristics of environmental factors (with wide range of trigger parameters) in patients with controlled asthma is weaker. This fact indicates the preservation of compensatory potential in this group of patients even in cold season. The influence

of the weather and man-made environment is pathogenic in uncontrolled asthma. In the city, the negative effect of air pollution by dust aerosols, especially fine fractions (0–1, 1–10 μm), and toxic metals (Co and Zn), which penetrate most deeply into the respiratory system, is formed against the background of the abrupt increase in weather sensitivity. The impact criteria of weather and man-made factors and the response ranges of PF significantly differ from average and standard values.

Further research is required in order to detail the seasonal impact of environment on respiratory patients living in Vladivostok.

Compliance with ethical standards

Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants complied with the ethical standards of Ethics Committee of the Vladivostok Branch of Federal State Budgetary Science Institution «Far Eastern Scientific Center of Physiology and Pathology of Respiration» – Institute of Medical Climatology and Rehabilitative Treatment (identification code of the protocol of the Ethics Committee: 10/12–11, approval date: December 07, 2011), and with the Declaration of Helsinki.

Conflict of interest The authors declare that they have no conflict of interest.

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