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Retinal Microvascular Response to Short-Term Exposure to Particulate Matters As an Indicator of Cardiovascular Effects in Work Environments

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ABSTRACT

Introduction: According to the literature, Central Retinal Arteriolar Equivalent (CRAE), Central Retinal Venular Equivalent (CRVE), and Artemio Venule Ratio (AVR) are three important markers in determining the changes of retinal artery. These markers are employed as an indicator of cardiovascular effects in workers. This study aimed to evaluate the changes in retinal micro vascular responses in workers exposed to short-term exposure to particulate matters caused by occupational processes using CRAE, CRVE, and AVR markers.

Materials and Methods: In this study, 96 workers exposed to job-related pollution in a tile and ceramic company were investigated. Fundus photos of these people were analyzed via ARIA software using the related protocols. The data were investigated employing Kolmogorov–Smirnov and Mann-Whitney tests as well as the correlation and regression tests.

Results: No significant difference was observed in the ocular parameters of smokers and non-smokers. Cardiovascular parameters had no significant correlation with CRAE and CRVE as well as breathable and inhalable dust; however, these parameters had a direct and significant correlation with AVR, PM_{10}, and $PM_{2.5}$ particles.

Conclusion: The results did not show any changes in the retinal artery in workers who were exposed to job-related pollution. Moreover, no significant relationship was found between retinal artery changes and cardiovascular parameters. However, more large-scale studies are needed to clarify the relationship of particulate air pollutants with CRAE, CRVE, and AVR changes.

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Introduction

Ischemic heart disease and stroke are the most common reasons of death in the US[1]. Heart diseases account for about 22 percent of the death rate across the world. Approximately 12 million people are suffering from this disease in the US. In Iran, cardiovascular diseases are considered as the first and most common causes of death at all ages in both males and females, so that of 700 to 800 daily deaths, 317 are due to cardiovascular diseases and 166 cases are due to heart attack, which mostly occur among people with 35 years of age and older [2]. Daily concentrations of air pollution and exposure to airborne pollutants, especially particulate matter ($PM_{2.5}$) are associated with a wide range of adverse health effects, especially

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mortality from cardiovascular and respiratory diseases[3-8]. Cardiovascular complications due to occupational exposure to various factors are among the strictest complications and diseases, which have been often neglected. Exposure to particulate matters, chemical substance, noise, smoking, physical activities, overtime, shift work, and job stress are some of the occupational risk factors that can increase the risk of cardiovascular diseases[5]. Particulate matter (PM) is one of the most dangerous risk factors that can disturb the blood circulatory system both directly and indirectly. In fact, PM exerts its indirect effect by disrupting the cardiac autonomic nervous system or inflammatory responses; while in the direct method, these particulate matters cause serious harm to blood vessels by entering the systemic blood circulation. Researchers believe that these particles decrease the capability of vessel walls to transfer blood to the heart, leading to cardiovascular diseases[9]. In addition to blood circulation in great arteries, microcirculation (defined as blood circulation in the smallest blood vessels) plays an important role in cardiovascular physiology and health[10]. Microcirculation, consisting of blood vessels with a diameter of less than 150µm, forms the major part of the cardiovascular system, delivers nutrients, eliminates metabolites, and exchanges gases (O_2 and CO_2) with body organs. Therefore, any disturbances in the cross-section of these vessels and presence of inflammatory factors will have direct consequences on their proper functioning[11, 12]. Capillary changes can be the primary symptom of the onset of cardiovascular diseases or a sign of their development[13]. Microcirculation plays an important role in regulating blood pressure. Diseases related to small arteries are also among the pathologic causes of high blood pressure[12, 14]. Toxicological studies show that $PM_{2.5}$ can disturb the process of capillary dilation through an interruption in their endothelium[3]. However, the relationship among changes in the microcirculation of small arteries (venules and arterioles) are not clear [15] because direct investigation and monitoring of microcirculation changes are difficult [9, 16] and conducted studies considering the relationship between exposure to air pollution and microcirculation changes are limited[10]. In this regard, investigating the involvement of small retina arteries with retinal imaging is a non-invasive in vivo method that provides the chance to study the changes in the small retinal capillaries (diameter of 60 – 300µm) [1, 17, 18]. In other words, many major diseases such as diabetes, diabetic retinopathy, and various types of apoplexy initially manifest themselves in the retina. The origin of these diseases in the eyes, brain, or cardiovascular system provides the opportunity for them to be studied and analyzed through eye imaging [19]. Given that workers are exposed to particulate matters in their workplaces, we aimed to study the retinal microvascular changesin short-term exposure to these particles using fundus photography.

Materials and Methods

The participants included 136 workers in one of the Tile and Ceramic companies in Meybod City of Yazd working in different sectors. Primarily, the workers' medical documents were studied and those without any history of cardiovascular, respiratory, ocular, and diabetic retinopathy diseases were selected. The criterion to enter the study was working in that industry for at least one year. Furthermore, all women workers were excluded due to the difference in investigated parameters. Finally, of 136 workers, 96 male workers with no history of the above-mentioned diseases were studied. Prior to the study, all participants were explained about the study procedures in details. Furthermore, they were asked to provide written informed consent forms to enter the study. The demographic features of the participants were collected through a researcher-made questionnaire.

Fundus photography

Analysis of the retinal images is an appropriate method to evaluate the responses of retinal microvessels to various factors in epidemiological studies. In order to take a fundus photo, the researcher was trained about the required points concerning the correct method of fundus photography in two weeks. After coordination with authorities in the factory, the researcher and health professional experts went to the study location and installed a fundus photo taker. Later, the participants were asked to go to a completely dark room prepared for fundus photography because fundus photography is highly sensitive to light. In this stage, a 45-degree CR-2 AF non-mydriatic 20.2-megapixel Canon camera was used to take a photo of the retina. Fundus photos were provided for both eyes of the participants that took 5 minutes at most. Each photo was visible by the monitor connected to the fundus camera. In the case that the participants did not meet the inclusion criteria or the photos were of low quality, they went through the test again. Moreover, for participants with small pupils, a mydriatic drop was used since taking photo of their eyes was not possible. The photos analysis was done according to the presented protocols and by Automated Retinal Image Analyzer (ARIA). As shown in figure 1, concentric circles were drawn from the margin of the optical disk with a distance 0.5 to 1 time more than the diameter of the optical disk using the correspondent software [20]. Later, the diameter of six largest arterioles and six largest venues in this zone were measured in micrometer.

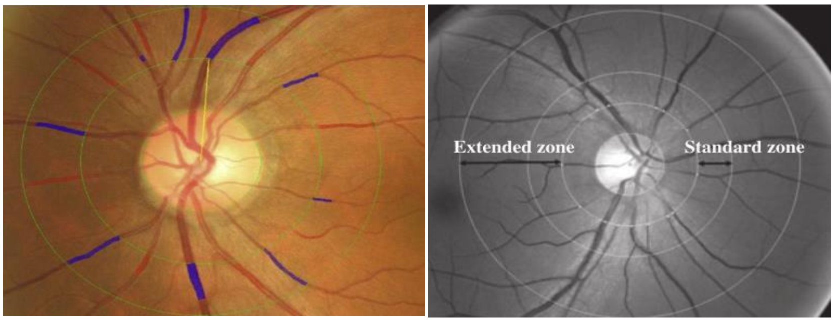

Figure 1: Zoning retina with a diameter of 0.5 to 1 time as the optical disc, blue venule, and red arteriole

The Parr-Hubbard formula and the results of measuring vessel diameter were applied and CRAE, CRVE, and AVR were calculated. To use this equation, the six measured vessels were sorted from large too small. Moreover, the largest and smallest vessels were placed in the correspondent equation pairwise. The result of these measurements was put in the same equation again to achieve a number for the intended variable. For instance, suppose that in a retina photo the diameters of 6 greatest vessels were 100, 90, 80, 70, 60, and 50, respectively. Initially, 100 and 50 were placed in the corresponding equation and x_1 was achieved. In the following, 90, 80, 70, and 60 were placed in the equation to achieve x_2 and x_3. Now, we sorted x_1, x_2, and x_3 from large to small and put them in the equation to achieve a similar answer [21].

Parr-Hubbard equation [22]:

For CRAE

$$W_{New} = (0.87\times W_{small}^2 + 1.01\times W_{large}^2 - 0.22\times W_{small}\times W_{large} - 10.76)^{0.5}$$

For the CRVE

$$W_{New} = (0.72\times W_{small}^2 + 0.91\times W_{large}^2 + 450.05)^{0.5}$$

W_{New}: The intended vessel diameter
W_{small}: The smallest vessel diameter
W_{large}: The largest vessel diameter

Particulate air pollutant sampling

To collect the study samples, real-time environmental sampling was applied. The monitoring was done in the real environment while workers were active in different sectors of the factory. The environmental measurements were calculated according to this formula based on the activity time in each line for each worker:

$$pm_{10} \text{ or } pm_{2.5} = \frac{(T1C1)+(T2C2)+ \dots + (TnCn)}{N}$$ [23]

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T: The time each person spends in each section per hour
C: Concentration of the measured particles in that section in milligram per cubic meter
N: Time shift of each person (8 hours)

The data were inserted in SPSS statistic 23 and the required analyses were done. The results were analyzed using descriptive statistics such as percentages, mean, standard deviation, and statistical tests such as Kolmogorov–Smirnov test, correlation, and Mann-Whitney test.

Ethical issue

This cross-sectional analytical study was conducted in the summer of 2017 after receiving the approval of the ethics committee (IR.SSU.SPH.REC.1395.107) of Shahid Sadooghi Medical University of Yazd.

Results

In this study, all participants were male. The workers' age and work experience mean and standard deviation were 34.93 ± 6.06 and 9.85 ± 4.62, respectively. Of all participants, 79.2 % were non-smokers and 20.8 % were smokers. To investigate the normality of variety distribution, Kolmogorov–Smirnov test was run; the findings showed that CRAE and CRVE variables followed a normal distribution. However, AVR did not follow a normal distribution (p-value = 0.040). The mean difference between CRAE and CRVE in the smoking and the non-smoking groups was investigated using T-student and ANOVA. Moreover, the AVR mean difference was analyzed using Mann-Whitney and Kruskal-Wallis in the study groups. The results revealed no significant difference between mean ocular parameters of smokers and non-smokers (p-value = 0.39, p-value = 0.40, p-value = 0.57). In table 1, the correlations between ocular parameters are mentioned by PM_{10}, $PM_{2.5}$, and heartbeat.

Table 1: Correlation of ocular parameters with particulate air pollutants and heartbeat

	Variables	Heartbeat	$PM_{2.5}$	PM_{10}
CRAE	Correlation coefficient	-0.034	0.010	0.105
	p-value	0.741	0.313	0.308
CRVE	Correlation coefficient	-0.041	-0.098	-0.071
	p-value	0.694	0.343	0.495
AVR	Correlation coefficient	0.006	0.223	0.223
	p-value	0.956	0.029*	0.029*

* Statistically Significant

According to the results of table 1, the correlation of AVR with PM_{10} and $PM_{2.5}$ was statistically significant with a direct relationship. However, no statistically significant correlation was found between particulate air pollutants and heartbeat. Table 2 shows the relationship of cardiovascular and ocular parameters with breathable and inhalable dust density in the rough model and the model justified with age, BMI, distance with major streets, and smoking at a significant level of 95%.

Table 2: Investigating the regression of particulate air pollutants' density with cardiovascular and ocular parameters

Valuables	Rough Model	p-value	Justified Model	p-value
CRAE	0.021(-0.024; 0.066)	0.362	(-0.033; 0.063) 0.015	0.535
CRVE	-0.017 (-0.083; 0.048)	0.603	(-0.099; 0.040) 0.030	0.398
AVR	0.0001 (-0.00002; 0.0003)	0.100	0.0001 (-0.00002: 0.0003)	0.086
[1]SBP	0.011 (-0.013; 0.035)	0.369	0.013 (-0.012; 0.039)	0.304
[2]DBP	0.007 (-0.009; 0.022)	0.422	0.009 (-0.008; 0.026)	0.290
[3]HR	-0.003 (-0.032; 0.026)	0.838	0.002 (-0.025; 0.03)	0.860

[1] Systolic Blood Pressure
[2] Diastolic Blood Pressure
[3] Heart Rate

According to the results, no significant relationship was found between the density of breathable and inhalable dust with cardiovascular and ocular parameters in the rough model and the justified model (justified with age, BMI, distance with major streets, and smoking). To investigate the relationship between ocular parameters and age, Pearson and Spearman correlation coefficients were used. For CRAE, CRVE, and AVE parameters, this coefficient was respectively 0.019, -0.035, and 0.1; none of which were statistically significant. Finally, ANOVA and Kruskal-Wallis tests were run to investigate the relationship between the mean of ocular parameters and workers' time shifts. According to the results, a statistically significant relationship was observed between CRVE and the workers' time shifts (p-value = 0.045). However, CRAE and AVR had no statistically significant relationship with the workers' time shift (p-value = 0.2, p-value = 0.3).

Discussion

To evaluate the effect of exposure to particulate air pollutants of workplaces on changes of retinal artery, three parameters of CRAE, CRVE, and AVR were assessed in a tile and ceramic factory by photography. Based on the findings, short-term exposure to PM_{10} and $PM_{2.5}$ caused by working processes did not have any significant effect on the changes in the retinal microvascular. In other words, vascular stenosis due to short-term exposure to pollutants in work environments is an independent parameter that cannot be used as an indicator of the risk of heart attack, hypertension, and mortality from vascular disease. However, the results of studies on the effect of particulate air pollutants on changes of workers' retinal arteries are contradictory. As an example, Louwies et al. pointed the statistically significant difference between retinal small vessels to short-term changes of PM_{10} in the air[10]. Moreover, Ljungman et al. stated the effect of exposure to particulate air pollutants on the changes of retinal artery[24]. This lack of association between short-term exposure to particulate matter and retinal microvascular changes can be justified through three explanations. 1- In this study, a control group (non-working population) in addition to the case group should have been considered to compare the findings between groups. We investigated the correlation between an independent variable with a limited range of changes (level of workers' exposure) and a variable dependent on the range of wide changes and found no significant results [25]. 2- The participants' lifestyle, as an effective marker on the results of our study, had a very wide range of changes affected by various conditions such as the distance of the participant's house from the crowded traffic area, duration of exposure to air pollutants during the non-working hours, type of food consumed, etc[26]. However, we could not determine and control the effects of these variables in this study. Given the contraction of small vessels of the retina, the peripheral resistance of the vessels does not change in general. As a result, blood pressure levels remain normal. However, microvasculature can be a target for early changes in blood vessels that can eventually affect blood pressure, leading to many related cardiovascular diseases [10]. Furthermore, we lacked the necessary facilities to control the factors affecting this marker. However, findings of the study conducted by Brook et al. are in line with our study, revealing that short-term exposure to particulate air pollutants cannot have significant effects on changing the diameter of retinal small vessels. Moreover, they noted that microvascular response to pollutant particles in the long-term exposure should be investigated[27]. So, the results of studies concerning changes of retinal small vessels in short-term and long-term exposure to particulate air pollutants need an evaluation of these parameters in large populations. Adar et al. study reinforces this hypothesis by noting that the short-term and long-term density of particulate matter had noticeable differences in terms of vessel capillaries in a sectional analysis of a large sample (Group of 4607 people)[3].Therefore was selected a larger target group as the study sample, which would be possible to achieve clearer and more accurate results.

Following some studies, it can be predicted that microvascular changes of the retina increase by increase of age [28]. In some other studies among the younger population, microvascular changes in the retina are more significant [23]. Rajagopalan et al. (2010) did not show any significant relationship between retinal microvascular changes in exposure to pollutants and increased cardiovascular mortality in people over 85 years of age. However, no significant relationship was found between age and ocular parameters in our study. Although we found no statistically significant relationship between CRVE and short-term exposure to particulate air pollutants, an inverse relationship was observed between CRVE and the density of particulate matter. In other words, exposure to a high density of breathable and inhalable particulates will result in a decrease in the CRVE parameter, which is in line with the findings of Louwies et al. [10]. On the other hand, Nawrot et al. believe that increasing the exposure time to particulate air pollutants such as Carbon black leads to a rise in CRVE ocular parameter [7].

Conclusion

Although air pollution can cause more physiological retinal microvascular changes, cardiovascular disorders, the amount of smoking, body mass index, age, etc. are among the factors that can affect the changes of retinal artery and lead to different findings in different studies. However, more studies are needed to clarify the relationship of particulate air pollutants with CRAE, CRVE, and AVR changes.

One limitation of this study is the lack of control over the confounding variables. This study supported the hypothesis that a concise investigation of retinal microvascular changes requires a very large sample size.

Overall, the results of this study showed that workers exposed to job-related particulate air pollutants had the lowest levels of retinal microvascular changes, while the rise in the retinal artery shows an increase in the probability of being affected by cardiovascular diseases.

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Conflict of interests

The authors declare no conflicts of interest regarding the publication of this paper.

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