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Vascular changes in the retina in patients with chronic respiratory insufficiency

Vaskularne promjene mrežnjače kod bolesnika sa hroničnom respiratornom insuficijencijom

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Abstract

Background/Aim. Chronic respiratory insufficiency is a pathological state which occurs as a result of respiratory system inability to maintain normal gas exchange between the outside air and circulating blood. For the purposes of human organism's proper functioning, it is necessary that a certain amount of air in the lungs comes into contact with a certain amount of blood within a unit of time, so that an adequate hemoglobin oxygenation could be achieved. Then, hemoglobin from erythrocytes in the blood supply delivers oxygen to all the tissues and cells of the body including the eye. Direct impact of hypoxemia and hypercapnia on the wall of arterioles, venules and capillaries results in a severe vasodilatation along with the increased permeability of the walls causing clinically evident changes in the retina. The aim of this study was to determine the degree of ocular changes in retina with patients suffering from chronic respiratory insufficiency. **Methods.** A prospective study was conducted on 80 patients, 40 patients with respiratory failure and 40 patients with chronic obstructive pulmonary disease an and bronchial asthma (the control group). In all the patients direct and indirect ophthalmoscopy and fluorescein angiography was performed. Clinically visible fundus and retina changes in patients suffering from chronic respiratory failure were categorized as mild (dilatation and retinal veins and arteries tortosion up to the mid-periphery), moderate (retinal hemorrhage) and severe (optic nerve edema, macular edema, superficial and deep retinal hemorrhages and venous occlusion). **Results.** In the patients suffering from respiratory insufficiency the changes in retinal blood vessels were found [in 18 (45%) mild, in 13 (32.5%) moderate, and in 9 (22%) severe], while in the patients with chronic obstructive pulmonary disease and bronchial asthma (without respiratory insufficiency) no changes were recognized. **Conclusion.** The results of this study indicate the need for ophthalmologic examination in patients with chronic respiratory insufficiency. It is important to recognize, identify and quantify the changes on retinal blood vessels which are clinically significant. It is necessary to provide their monitoring and to prescribe proper therapeutic treatment in order to preserve visual functions.

Key words:
respiratory insufficiency; pulmonary disease, chronic obstructive; anoxia; retinal disease; optic nerve.

Apstrakt

Uvod/Cilj. Hronična respiratorna insuficijencija je patološko stanje koje nastaje kao posljedica nesposobnosti respiratornog sistema da održava normalnu razmjenu gasova između spoljnog vazduha i cirkulišuće krvi. Za potrebe organizma neophodno je da određena količina vazduha u plućima dođe u kontakt sa određenom količinom krvi u jedinici vremena, radi adekvatne oksigenacije hemoglobina. Dalje, hemoglobin u eritrocitima krvnom strujom doprema kiseonik do svih tkiva i ćelija organizma, pa i oka. Direktnim dejstvom hipoksemije i hiperkapnije na zid arteriola, venula i kapilara, nastaje izrazita vazodilatacija uz povećanu permeabilnost zidova usled čega nastaju klinički vidljive promjene na retini. Cilj ovog rada bio je da se utvrdi stepen oftalmoloških promjena na retini kod bolesnika sa hroničnom respiratornom insuficijencijom. **Metode.** Sprovedena je prospektivna studija koja je obuhvatila 80 bolesnika, 40 sa respiratornom insuficijencijom i 40 oboljelih od hronične opstruktivne bolesti pluća i bronhijalne astme (kontrolna grupa). Oftalmološki pregledi su vršeni direktnom i indirektnom oftalmoskopijom, a po potrebi rađena je i fluoresceinska angiografija. Klinički vidljive promjene na očnom dnu, odnosno retini, kod bolesnika sa hroničnom respiratornom insuficijencijom, klasifikovane su kao blage (dilatacija i tortoznost retinalnih arterija i vena do srednje periferije), umjerene (retinalne hemoragije) i teške (edem optičkog nerva, makularni edem, površna i duboka retinalna krvarenja i venske okluzije). **Rezultati.** Kod bolesnika sa respiratornom insuficijencijom nađene su promjene na retinalnim krvnim sudovima

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[kod 18 (45%) lake, kod 13 (32,5%) umjerene i 9 (22,5%) teške], dok kod bolesnika sa hroničnom opstruktivnom bolešću pluća i bronhijalnom astmom (bez respiratorne insuficijencije) promjene nisu nađene. **Zaključak.** Rezultati ovog istraživanja ukazuju na potrebu oftalmološkog pregleda bolesnika sa respiratornom insuficijencijom. Važno je da se uoče, prepoznaju i kvantifikuju klinički značajne promjene na krvnim sudovima retine. Neophodno je njihovo praćenje i odabiranje adekvatnog terapijskog lečenja u cilju očuvanja vidne funkcije.

Ključne reči:
respiratorna insuficijencija; pluća, opstruktivne bolesti, hronične; anoksija; retina, bolesti; n. opticus.

Introduction

Respiratory insufficiency is an ill condition that is the result of respiratory system inability to transmit normal exchange of respiratory gases between the outside air and circulating blood [1–4]. It is characterized by a decreased partial pressure of oxygen (PaO_2) (hypoxemia) in arterial blood and reduced saturation (hyposaturation) with hemoglobin oxygen (SaO_2), with normal or elevated partial pressures of carbon dioxide ($PaCO_2$) (hypercapnia).

If the breathing process is properly conducted, arterial values PaO_2, $PaCO_2$ and pH will be in the physiological range. Hypoxemia includes a reduced PaO_2 in arterial blood below 9.3 kPa on average (normal pressure depends on age), hemoglobin saturation below 0.94, while the occurrence of hypercapnia is the elevated partial in arterial blood over 6 kPa. [5, 6]. Respiratory insufficiency may be acute or chronic.

The natural course of chronic respiratory failure is characterized by occasional acute deteriorations, which is called respiratory decompensation. Acute deterioration of chronic respiratory failure is defined through finding of respiratory gases in arterial blood when $PaO_2 < 50$ mmHg and/or $PaCO_2 > 50$ mmHg [2, 6, 7].

Signs and symptoms of pulmonary insufficiency are manifested at the stage of pulmonary decompensation. Severe hypoxemia and hypercapnia lead to many metabolic, circulatory, respiratory, enzymatic, endocrine and hematologic disorders. Facies of patients get polyglobulic, pletoric and cyanotic look.

Hyperemia of the conjunctiva and sclera is fully shown, often exophthalmia, bloatedness and sweating over the entire face, particular glow in the eyes that get brilliant, and tearful appearance called "frog faces" can be observed.

Ophthalmologic examination shows dilated and visible, tortoise blood vessels of retina, superficial and deep retinal hemorrhages with macular and papillary edema [8, 9].

Three basic changes in arterial blood resulting in chronic pulmonary insufficiency are hypoxemia, hypercapnia, changes in acid-base balance in the direction of acidity. They affect retinal blood vessels in terms of alterations in blood flow.

The eye allows visualization of its circulation [10–14]. The retina is translucent, and the visible part of the retina is intraretinal vascular stem. Alterations that attack the intraretinal vascular stem caused by arterial hypertension, arteriosclerosis, diabetes mellitus, sickle cell disease, and conditions such as hyperviscosity, embolic and thrombotic phenomena, can be observed [15]. The eye is a complex organ that has a number of different microcirculation systems to help its needs. Structural, neurological and permeability differences can be found in different intravascular microcircular structures. Micro blood vessels in every type of tissue continuously monitor the needs of tissue, such as nutrition and accumulation of harmful products in the tissues, which in turn controls local blood flow with great precision at a level appropriate to the activities of tissue. Also, the neural control provides additional attributes for controlling the flow of blood [11, 16]. The vasodilator theory of blood flow local regulation indicates that the higher metabolic activity and the lower blood flow or lesser delivery of oxygen and nutrients into the tissue substrate, the more quickly vasodilator substances are generated. It is considered that the vasodilator matters could be: adenosine, CO_2, lactate, ADP, histamine, K^+ ions, H^+ ions. They diffuse to precapilar structures (meta-arterioles and arterioles) and cause vasodilatationm [17]. The theory of metabolic control of the local flow is based on tissue requirements for oxygen and other nutritive substances. When the delivery of oxygen and other nutritive substances is inadequate, blood vessels dilate themselves. Thus, in the kidneys and the brain local control of blood flow depends on tissue concentration O_2, CO_2 and H_2 [18].

The aim of this study was to determine the degree of retinal vascular changes in patients with chronic pulmonary insufficiency, in order to estimate any correlation between the severity of clinical signs on the retina and the severity and deterioration of hypoxemia and hypercapnia, as well as to clearly differentiate clinical and morphological changes of the retina caused by hypoxemia and hypercapnia.

Methods

The study included a total of 80 patients, 40 patients with chronic pulmonary disease and 40 patients with chronic obstructive pulmonary disease (COPD) and bronchial asthma (the control group). The survey was conducted at the Ophthalmology Clinic in Podgorica, Specialized Hospital for Lung Diseases in Brezovik, Department for Pulmonology and Clinical Center of Montenegro, Podgorica, in the period from January 2009 to January 2011, and in patients who also were treated in the Pulmonary and Ophthalmology Institutes of Clinical Center of Serbia, Belgrade. The survey was conducted with the approval of the Ethic Committee of the above mentioned institutions.

The study consisted of laboratory and clinical phases testing. The subjects with chronic respiratory failure were in different conditions, from those with stable conditions to those with acute deterioration. The participants of the control

group had COPD and bronchial asthma. The laboratory phase included analysis of $PaCO_2$ and PaO_2 in arterial blood. The measurement of these parameters was performed by taking a blood from brachial and radial arteries or peripheral parts of the body (fingertip and earlobe). Clinical-stage testing included biomicroscope eye bottom scan with lenses, indirectly; ophthtalmological examination, and examination of the eye contact Goldmann bottom glass with three mirrors, and, finally, fluorescein angiography (FA) – a diagnostic method that is used for the interpretation of pathological conditions of the eye. FA is a method to show the vascular structures of various layers of retinal tissue and analyze the dynamics of circulation. FA is not only diagnostic technique, but also a way of controlling the evolution of lesions on the retina, in the same time being a help in the therapeutic indication, especially in retinal laser photocoagulation. By ophthalmologic eye examination, we classified the bottom changes to mild, moderate and severe. Retinal-vascular changes are the result of interaction of hypoxemia, hypercapnia, and clinically are visible as: segmented, tortuous, large and dilated retinal blood vessels (mild changes) retinal hemorrhages (moderate changes) and optic nerve papilloedema, macular edema, superficial and deep retinal hemorrhages and venous occlusion of blood vessels (severe changes).

The subjects were divided into three groups based on the presence of retinal-vascular changes.

Statistical data analysis was performed using χ^2 test to estimate the statistical significance of differences in the frequency of occurrence of certain characteristics in the study and the control group and between them. The value of $p < 0.05$ was considered statistically significant.

Results

This study included a group of 40 patients with chronic pulmonary insufficiency (the study group) and the control group (40 patients) with COPD and bronchial asthma.

The analysis of demographic data shows that in the study group most patients were aged 60 to 69, and in the control group between 40 and 49 (Table 1), while in terms of gender in both groups the majority were men (Table 2).

Table 1

Demographic characteristics by the groups

Age (years), range	Men (n)	Women (n)	Total (n)
Study group			
50–59	9	2	11
60–69	11	6	17
70–79	8	4	12
Control group			
30–39	6	4	10
40–49	14	8	22
50–59	3	3	6
60–69	1	1	2
70–79	0	0	0

Study group – patients with chronic respiratory insuficiency;
Control group – patients with chronic obstructive pulmonary disease and asthma.

Table 2

The subjects of the study and the control group by gender

Groups of patient	Sex, n (%)		Total
	male	female	n (%)
Study	28 (53.85*; 70†)	12 (42.86*; 30†)	40 (50*; 100†)
Control	24 (46.15*; 60†)	16 (57.14; 40†)	40 (50*; 100†)
Total	52 (100*; 65†)	28 (100*; 35†)	80 (100*; 100†)

Study group – patients with chronic respiratory insuficiency;
Control group – patients with chronic obstructive pulmonary disease and asthma.
*** – vertical; † – horizontal.**

There were no statistically significant differences between the study and the control group in relation to gender ($p > 0.05$). The ratio of men and women between the study and the control group was 53.85%: 46.15% and 42.86%: 57.14%, respectively.

Analysis of respiratory gases in arterial blood in the study group showed that the value of the partial pressure of oxygen (PaO_2) less than 50 mmHg was present in 77.5% of the subjects, and $PaCO_2$ values of more than 60 mmHg in 85% of participants which corresponds to acutisation of chronic respiratory failure. Only 15% of the participants of the study group had $PaCO_2$ values < 60 mmHg (Table 3).

In the control group, the average values of PaO_2 were 65.24 mmHg in men and 65.03 mmHg in women, and average values of $PaCO_2$ 36.11 mmHg in men and 36.40 mmHg in women.

Therefore, we analyzed the changes found in blood vessels of the retina in the 40 patients of the study group. The analysis showed that 45% of the patients in the study groups had mild forms of changes, 32.50% moderate changes, and 22.50% severe changes (Table 4).

Table 3

The values of partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) of the study group participants according to gender

Partial pressure of O_2 and CO_2 in arterial blood (mmHg), range	Sex, n (%)		Total n (%)
	male	female	
PaO_2			
35–39	12 (42.86*; 100†)	0 (0*; 0†)	12 (30*; 100†)
40–44	6 (21.43*;60†)	4 (33.33*; 40†)	10 (25*; 100†)
45–49	5 (17.86*; 55.56†)	4 (33.33*; 44.44)	9 (22.15; 100†)
50–54	3 (10.71*; 60.5†)	2 (16.67*; 40†)	5 (12.5; 100†)
55–59	2 (7.14*; 66.67†)	1 (8.33*; 33.33†)	3 (7.5; 100†)
60–64	0 (0*; 0†)	1 (8.33*; 100†)	1 (2.5; 100†)
65–69	0 (0*; 0†)	0 (0*; 0†)	0 (0*; 0†)
Total	28 (100*; 70†)	12 (100*; 30†)	40 (100; 100†)
$PaCO_2$			
30–39	0 (0*; 0†)	0 (0*; 0†)	0 (0*; 0†)
40–49	0 (0*; 0†)	0 (0*; 0†)	0 (0*; 0†)
50–59	3 (10.71*; 50†)	3 (25*; 50†)	6 (15*; 100†)
60–69	5 (17.86*; 45.45†)	6 (50*; 54.55†)	11 (27.5*; 100†)
70–79	2 (7.14*; 66.67†)	1 (8.33*; 33.33†)	3 (7.5*; 100†)
80–89	9 (32.15*; 81.82†)	2 (16.67*; 18.18†)	11 (27.5*; 100†)
90–99	4 (14.29*; 100†)	0 (0*; 0†)	4 (10*; 100†)
100–109	3 (10.71*; 100†)	0 (0*; 0†)	3 (7.5*; 100†)
110–119	2 (7.14*; 100†)	0 (0*; 0†)	2 (5*; 100†)
Total	28 (100*; 70†)	12 (100*; 30†)	40 (100*; 100†)

Study group – patients with chronic respitratory insufficiency.
*** – vertical; † – horizontal**

Table 4

The degree of changes in the retina of the patients in the study group

Degree of retinal changes	Sex, n (%)		Total n (%)
	male	female	
No	0 (0*; 0†)	0 (0*; 0†)	0 (0*; 0†)
Mild	9 (31.24*; 50†)	9 (75*; 50†)	18 (45*; 100†)
Moderate	10 (35.72*; 76.92†)	3 (25*; 23.08†)	13 (32.5*; 100†)
Severe	9 (32.14*; 100†)	0 (0*; 0†)	9 (22.5*; 100†)
Total	28 (100*; 70†)	12 (100*; 30†)	40 (100*; 100†)

Study group – patients with chronic respitratory insufficiency.
*** – vertical; † – horizontal**

Discussion

Our study showed that in patients with chronic respiratory insufficiency there were changes in retinal blood vessels. These changes are the result of hypoxemia and hypercapnia in retinal blood vessels. Hypoxemia and hypercapnia occur as a result of permanent damage of lung function in chronic respiratory insufficiency [7].

Small changes in oxygen concentration cause changes in blood flow in large diameter retinal blood vessels. Hypercapnia has larger impacts on the macular flow increasing it to 24%. The similar happens in large blood vessels, but it does not change the diameter of blood vessels. Chronic hypoxemia causes slight changes in the retina, which are reflected in segmented dilatation and tortuosity of large retinal blood vessels [15, 17].

The interactive action of hypoxemia and hypercapnia causes moderate changes in the retina (retinal hemorrhage) when sudden outbreak of hypoxemia and hypercapnia, papilloedema of the optic nerve and macular edema appear, together with superficial and deep retinal hemorrhage and thrombosis.

Our study included 80 patients, 40 of whom were chronic pulmonary insufficiency, and 40 with COPD and bronchial asthma and in stable condition without a significant respiratory insufficiency. The research showed that pulmonary disease may in the course of its evolution lead to permanent damage of lung function, and in the terminal stage to chronic pulmonary failure.

The study group was dominated by men (70%). In the control group there was 60% of men, and 40% of women. These relationships do not indicate any statistically significant differences between the groups in relation to gender. The data provided correspond to those listed in our bibliography [1, 2, 6].

Lung diseases presented in our patients are widespread in both industrialized countries and in developing countries. Smoking habits, environmental pollution, substandard housing conditions and working environment, rapid urbanization, contribute to causes of these lung diseases. These diseases are undoubtedly more common with adult men.

However, in recent years more and more women suffer because of the widespread habit of smoking.

In the study group the patients were mainly adults between 50 and 79. Most of them were in the age group between 60 and 69, 17 (42.50%), and the fewest in the age group between 50 and 59, 11 (27%). In the control group there were adults of the age of 30 and 70. Most sufferers were in the age group between 40 and 49, 22 (55%), the fewest were in the age group between 60 and 69, 2 (5%). This finding is analogous to the findings in the bibliography [17, 19].

Chronic pulmonary insufficiency occurs in adults and elderly population, together with COPD, while bronchial asthma is prevalent in younger population.

Examining PaO_2 values in relation to sex, it can be concluded that the distribution of respondents by PaO_2 was very uneven. In the study group the values of PaO_2 up to 50 mm Hg were present in 77.5% of respondents, and more than 50 mm Hg in 22.5% of them.

In the control group subjects had no significant respiratory failure, and the average value of PaO_2 for men was 65.24 mm Hg and for women 65.03 mm Hg.

In the study group PaO_2 was less than 50 mm Hg in 77.5% of the patients, while in the control group none of the participants had the PaO_2 lower than 65 mmHg. This explains the nature and course of lung disease.

Chronic pulmonary insufficiency is a condition with severely impaired lung function, varying degrees of hypoxemia, and/or hypercapnia, whereas in COPD and bronchial asthma, there is a slight disturbance in arterial blood gases in stable condition [5, 20, 21].

In the study group $PaCO_2$ values up to 60 mmHg were present in only 15% of the patients. In the control group, all subjects had lower $PaCO_2$ of 45 mmHg (the average values of $PaCO_2$ were 36.11 mmHg for men and 36.40 mmHg for women).

It was observed that in the study group due to hypoxemia and hypercapnia there were changes in the retinal blood vessels in all patients. Most of the respondents had a mild form of changes, 18 or 45%, followed by the moderate changes, 13 or 32.5%, while heavy changes had 9 (22.5%) of the patients. In the control group, since there were no significant disturbances of respiratory gases, no respondent showed any changes in the retina. Our findings are similar to those of American authors [10, 11].

The results of this study on the changes in blood vessels of the eye bottom in patients with chronic respiratory failure indicate the need for the same ophthalmologic examination, monitoring and selecting the appropriate therapeutic procedure [22, 23].

With the correct interpretation of clinical findings, an ophthalmologist should act timely to: recognition, control and monitoring of retinal vascular changes in patients with chronic respiratory insufficiency, setting the indications for laser photocoagulation, and setting the indication for fluorescein angiography [24, 25].

Treating patients with severe changes is a particular problem because of the threat visual function. It is possible to maintain a satisfactory visual retinal function with an adequate laser photocoagulation applied timely.

Conclusion

The results of this study indicate the need for ophthalmologic examination in patients with chronic respiratory insufficiency.

Early detection, monitoring and selection of patients for active treatment is of a major importance in the treatment of severe retinal-vascular changes in patients with chronic respiratory insufficiency in the stage of decompensation.

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