

Evaluation of Arterial Blood Flow Changes by Orbital Doppler in Chronic Obstructive Pulmonary Disease and Asthma

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Purpose: Both chronic obstructive pulmonary disease (COPD) and asthma are important causes of morbidity and mortality worldwide. They primarily affect the lungs, but they have various extrapulmonary manifestations. The aim of our study was to evaluate the hemodynamic changes in orbital vessels of the patients with COPD and asthma using color Doppler ultrasonography and compare the results with healthy control subjects.

Methods: Thirty-seven patients with COPD, 37 patients with asthma, and 41 healthy control subjects were included in this study. All patients with COPD were in moderate to severe group according to GOLD (Global Initiative for Chronic Obstructive Lung Disease), and similarly, all patients with asthma were in moderate to severe persistent group according to GINA (Global Initiative for Asthma) 2006 guidelines. End-tidal carbon dioxide, peripheral oxygen saturation, pulse rate, and respiratory rate were measured by using pulse oximeter in all patients. Measurements were performed in only 1 randomly selected eye of each participant. The peak systolic velocity, end diastolic velocity, and resistance index were measured in the central retinal artery, temporal posterior ciliary artery, and nasal posterior ciliary artery using the color Doppler ultrasonography technique.

Results: The peak systolic velocity, end diastolic velocity, and resistance index values of temporal posterior ciliary artery and nasal posterior ciliary artery were significantly higher in COPD and asthma than in the control subjects. There was no difference between asthma and COPD.

Conclusions: We concluded that retrobulbar hemodynamics change in COPD and asthma is showing 1 of the systemic effects in these diseases.

Key Words: orbital Doppler ultrasound, COPD, asthma

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Chronic obstructive pulmonary disease (COPD) and asthma are both characterized by chronic persistent inflammation of the airways and lung. The main reason for this inflammation in COPD is the exposure to inhaled irritants such as tobacco, and the main reason for this inflammation in asthma is the allergic reaction to the inhaled aeroallergens. The inhaled irritants activate inflammatory cells, which initiate an inflammatory cascade as follows: the triggering of the production of inflammatory

mediators such as C-reactive protein (CRP), interleukins, and fibrinogen; release of leucocytes and thrombocytes from the bone marrow; and activation of the leucocytes and vascular endothelial cells in the circulation.¹ Oxidative stress is evident in the lung tissue and systemic circulation because inflammatory cells are activated and proinflammatory cytokine levels are increased. These inflammatory mediators sustain the inflammatory process and lead to tissue damage as well as a range of systemic effects. The clinical manifestations of COPD are not only restricted to pulmonary inflammation, but also significant systemic effects can be seen in other organs and blood profile. Both COPD and asthma have various extrapulmonary manifestations including muscular dysfunction and hypotrophy, cachexia, or cardiovascular complications.² Owing to these reasons, they should be considered as systemic diseases.

Asthma is a chronic airway inflammation that involves the interplay of different types of inflammatory cells such as eosinophils, lymphocytes, mast cells, and cytokines in the airway.³ Activation of inflammatory cascades leads to hyperresponsiveness of the airways, with consequent lower airflow obstruction and breathing difficulties. Beside local inflammation, systemic inflammation is also present, which can be determined by increased levels of CRP.⁴ Spillover of inflammatory mediators into the circulation is generally considered to be the source of this systemic inflammation. Despite this hypothesis, the nature of systemic inflammation in COPD and asthma still remains unclear.⁵

In patients with COPD and asthma, systemic inflammation is considered as a key factor in the pathogenesis of the multi-component disease manifestations.

Ocular complications can also be seen in COPD and asthma patients.⁶ Color Doppler ultrasound (CDU) is a noninvasive imaging technique that gives information on ocular hemodynamics. Measuring ocular blood flows by CDU have been used for the diagnosis of different orbital and systemic pathologies. However, only a few data exist about the effects of chronic hypoxia or hypercapnia on ocular arteries in COPD and asthma patients. Luksch et al.⁷ investigated the effects of inhalation of different mixtures of O₂ and CO₂ levels in retinal blood flow. Ozer et al.⁸ showed the alterations in ocular blood flow among COPD patients in a previous study. To the best of our knowledge, there are no published data on the Doppler ultrasound examination of ocular circulation in asthma patients. Asthma and COPD are both COPDs with only a difference that the airway obstruction in asthma is usually reversible. The purpose of our study was to evaluate the flow velocity and resistive changes in the ocular circulation of COPD and asthma patients and to compare Doppler findings of these patients with control subjects.

MATERIAL AND METHODS

After obtaining approval from the institutional review board and written informed consent from patients and control subjects, this study enrolled a total of 115 subjects. Thirty-seven

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TABLE 1. General Characteristics of Study Participants

	COPD	Asthma	Control	P	COPD-Asthma	COPD-Control	Asthma-Control
Age, mean (SD), y	64.11 (7.39)	59.84 (12.95)	59.17 (12.31)	0.119	0.312	0.163	1.0
Sex, F/M	22/15	31/6	30/11	0.065	0.60	0.525	0.879

F, female; M, male.

patients (22 females and 15 males) aged between 50 and 89 years (mean [SD], 64.11 [7.39] years) with COPD, 37 patients (31 females and 6 males) aged between 37 and 83 years (mean [SD], 59.84 [12.95] years) with asthma, and 41 healthy individuals (11 males and 30 females) aged between 23 and 81 years (mean [SD], 59.17 [12.31] years) were prospectively evaluated (Table 1).

Pulmonary function tests were performed to determine the forced vital capacity (FVC), forced expiratory volume in first second (FEV1), and FEV1/FVC ratio. Chronic airflow obstruction was defined as FEV1/FVC ratio less than 70%. Patients with COPD were diagnosed and classified according to the GOLD (Global Initiative for Chronic Obstructive Lung Disease)⁹ as follows: stage I COPD (mild airflow limitation) (FEV1/FVC < 70%, FEV1 ≥ 80%), stage II COPD (worsening airflow limitation) (FEV1/FVC < 70%, 50% ≤ FEV1 < 80%), stage III COPD (severe airflow limitation) (FEV1/FVC < 70%, 30% ≤ FEV1 < 50% predicted value), or stage IV COPD (very severe airflow limitation) (FEV1/FVC < 70%, FEV1 < 30% predicted value). Stage II and III COPD patients were enrolled into the study. Stage IV patients were not included in the study because they could alter the study results. Similarly, all patients with asthma were in moderate to severe (persistent) group according to the GINA (Global Initiative for Asthma) 2012 guidelines. The severity of symptoms, clinical findings, the need for frequent rescue medications, and the frequency of unscheduled emergency visits were evaluated for classification.¹⁰

Complete blood count, blood chemistry profile, and neurological examination of all participants were obtained to detect any other systemic disease. Blood pressure was measured for all participants before CDU examination. The routine ophthalmologic examination was performed in all patients including visual acuity, anterior segment, and fundus examination with intraocular pressure measurement. Patients with any known disease to affect blood flow, such as polycythemia, vasculitis, systemic vascular disease, diabetes, astigmatism greater than 2 diopters, aphakia or pseudophakia, and patients with an intraocular pressure greater than 21 mm Hg were not included in the study.

Forty-one age-matched healthy volunteers who had no history of ophthalmic pathology, with a normal optic disc and intraocular pressure, were included in the control group. All of the patients or control subjects did not have a history of major systemic diseases, including left heart failure, arterial hypertension, or diabetes mellitus. Ex-smokers that did not smoke within 1 year and nonsmokers were included into the study, and current smokers were excluded to eliminate smoking effects. Subjects were informed not to take caffeine and other known vasoconstrictive compounds for at least 24 hours before CDU examination. Subjects had been using 1 or more of the following drugs: β2-agonists (salbutamol, salmeterol, formoterol), anticholinergic (tiotropium), and methylxanthine.

The same radiologist experienced in Doppler ultrasound for 5 years performed all measurements by using color Doppler on a Sonoline Antares sonographic system (Siemens AG, Munich, Germany) with a vibration frequency 13–5 MHz transducer.

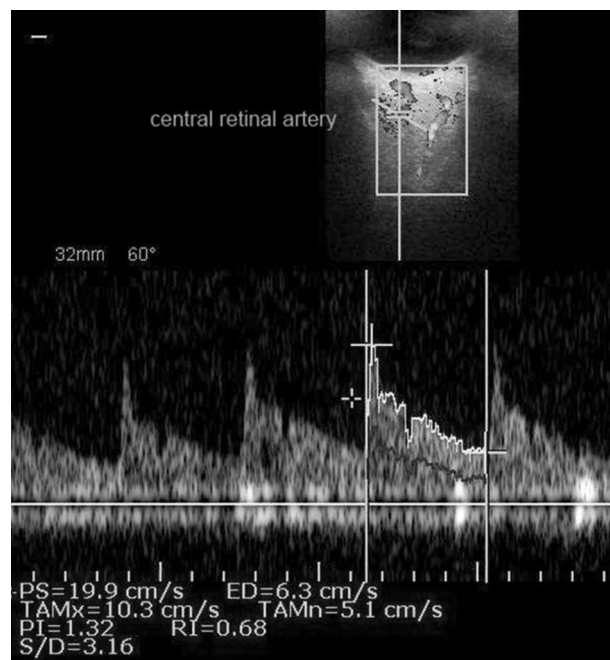
Ultrasound gel was gently applied to the external surface of the upper eyelid, and care was taken to avoid applying any pressure to the orbit. The central retinal artery (CRA), nasal posterior ciliary artery (NPCA), and temporal posterior ciliary artery (TPCA) were examined in each subject. All measurements were done with an angle-correction cursor that was adjusted parallel to the direction of blood flow (with a limit of 60 degrees).

The TPCA and NPCA were visualized immediately posterior to the globe and lateral to the optic nerve shadow. The CRA was visualized within the retrolaminar portion of the optic nerve where the vessel maintains a straight course (Figs. 1 and 2).

The following data were recorded for each of the previously mentioned arteries: (a) peak systolic flow velocity (PSV) defined as the highest velocity of the blood flow during the systolic phase of 3 cardiac cycles; (b) end-diastolic flow velocity (EDV) defined as the velocity of blood flow at the end of diastolic phase of the cardiac cycle; and (c) resistive index (RI) defined as (PSV – EDV)/PSV (Table 2).

Statistical Analysis

Data were analyzed using parametric and nonparametric tests as appropriate with SPSS software 16.0 programs (SPSS, Chicago, IL). Repeated measures analyses of variances followed by post hoc analyses with Bonferroni adjustment were used to compare the statistical distribution of parameters measured. The results of measurements were expressed as mean

**FIGURE 1.** Doppler spectrum of CRA from the control group.

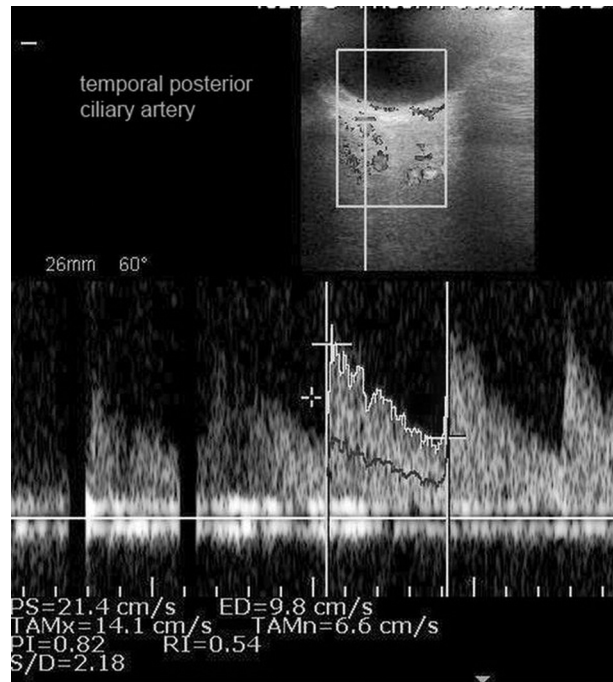


FIGURE 2. Doppler spectrum of TPCA from the control group.

(SD). *P* values of less than 0.05 were considered to be statistically significant.

RESULTS

There were no significant differences between COPD or asthma patients and the control group in regards to age ($P = 0.11$).

The PSV, EDV, RI of TPCA, and NPCA were higher in both COPD and asthma groups than in the control group, and the difference was statistically significant. There was no statistically significant difference regarding these values between COPD and asthma subjects. The EDV of CRA was higher in asthma group than in the controls. The RI of CRA was higher in the COPD group than in the controls. The EDV of CRA did not differ significantly between the COPD and control groups. There was no statistically significant difference in EDV values between COPD

and controls. The RI of CRA was not significantly different in asthma patients compared with that in the control subjects.

DISCUSSION

Providing the oxygen necessary for the optimal functions of all cells, tissues, and organs in the body and discharging carbon dioxide from the body, which is produced by the metabolic activities, are the main functions of the lungs. In diseases causing any defects in delivering enough oxygen to the tissues and/or causing any increase in carbon dioxide levels in blood, some insufficiencies in functions of other organs and development of structural defects or some other diseases are possible. Chronic obstructive pulmonary disease is a disease that is characterized by a progressive airflow limitation. In severe forms, parenchymal destruction and pulmonary vascular abnormalities are also seen, which reduce the lung's capacity for gas exchange, producing systemic hypoxemia and later on hypercapnia.¹¹ Oxidative stress and neurohormonal activation can also be detected in patients with COPD.

A relative oxygen deficiency may provoke a compensatory increase in blood flow velocity for meeting metabolic demand.^{9,12} Augmented PSVs of orbital arteries in our COPD and asthma patients may be the result of this regulatory mechanism.

We found higher PSVs and EDVs in TPCA and NPCA in moderate to severe COPD and asthma patients. Although eye Doppler ultrasound values were higher in both asthma and COPD patients than normal controls, there were no differences between asthma and COPD patients. Similarly, Ozer et al.⁸ found that the PSVs in the CRA, lateral posterior ciliary artery, and medial posterior ciliary artery were slightly higher in groups II and III than in the control group, but the difference was not statistically significant. Maclay et al.¹³ showed an increased arterial stiffness independent of cigarette smoke exposure in COPD patients. However, they explained this abnormality not by systemic endothelial dysfunction, mostly by increased arterial stiffness due to mechanistic link between COPD and the increased risk for cardiovascular disease associated with this condition. More studies are needed to elucidate the main mechanism for these vascular changes.

In all studies done with Doppler ultrasound, blood flow volume in ocular arteries are not measured because blood flow volume can only be measured if the diameter of the vessel is known (it equates to the blood flow velocity $\times$ the cross-sectional area of the vessel). These vessels were too small in diameter to permit precise measurement of the cross-sectional area.

TABLE 2. Arterial Blood Flow Velocities Determined by Doppler Ultrasound

	COPD	Asthma	Control	<i>P</i>	COPD-Asthma	COPD-Control	Asthma-Control
NPCA							
PSV	16.66 (3.38)	16.40 (2.81)	13.72 (2.10)	<0.001	1.0	<0.001	<0.001
EDV	6.31 (1.54)	6.40 (1.66)	5.47 (1.27)	0.011	1.0	0.041	0.020
RI	0.64 (0.05)	0.63 (0.06)	0.59 (0.07)	0.004	1.0	0.007	0.025
TPCA							
PSV	18.90 (3.88)	18.37 (3.81)	14.62 (2.32)	<0.001	1.0	<0.001	<0.001
EDV	7.09 (2.03)	6.87 (1.67)	5.81 (1.23)	0.002	1.0	0.003	0.019
RI	0.65 (0.07)	0.63 (0.06)	0.59 (0.08)	0.001	1.0	0.001	0.024
CRA							
PSV	14.66 (2.79)	15.64 (3.23)	12.96 (1.86)	<0.001	0.353	0.017	<0.001
EDV	5.08 (1.17)	5.58 (1.59)	4.74 (1.16)	0.021	0.309	0.784	0.017
RI	0.68 (0.05)	0.65 (0.06)	0.62 (0.06)	<0.001	0.104	<0.001	0.114

P values that are statistically significant are written in bold.

In the present study, we found higher resistance indices in orbital arteries of COPD and asthma patients compared with the normal controls. Similarly, Ozer et al.⁸ found that the RI values of CRA in groups II and in group III were significantly higher than that of control subjects ($P < 0.05$). The RI values of LPCA and MPCA in group II were also found to be significantly higher than those of controls ($P < 0.05$). The results of that study showed an increased vascular resistance in orbital arteries of COPD patients with increased retrobulbar blood flow.

The resistance index is angle independent and considered to show vascular resistance peripheral to the measuring location.¹⁴

It was shown that endothelin-1 (ET-1) levels are increased in plasma, sputum, and urine samples of COPD patients, compared with that in controls.^{15,16} The increased concentrations of ET-1 in plasma of asthmatic patients were also demonstrated in some recent studies.^{17,18} Endothelin-1 is released by alveolar epithelial cells, vascular endothelial cells, and inflammatory cells such as macrophages and mast cells.¹⁹ It is known as a potent vasoconstrictor.

Polak et al.²⁰ revealed a dose-dependent vasoconstrictor effect of ET-1, mainly on the microvessels of the retina. It was speculated that increased plasma levels of ET-1 may result in vasospasm, causing an increase in resistance to ocular artery blood flow in COPD patients. Elevated plasma ET-1 levels in COPD and asthma patients are likely to be related to chronic hypoxia. One of the limitations of our study was that we did not measure inflammatory indices in plasma so we could not search the relationship between inflammation and CDU.

Atherosclerosis has been reported with an increasing frequency among patients with COPD. In a study evaluating the ocular complications in patients with severe COPD, Tunc and et al.⁶ found that the second most common ocular finding was the atherosclerotic changes in retinal vessels (35%).⁸ Sun et al.²¹ determined the brachial-ankle pulse wave velocity as a marker for early atherosclerotic changes among patients with persistence asthma, and they showed a significant increase in CRP among those patients. Weiler et al.²² found a positive correlation between asthma and on early vascular changes in young patients with asthma. Atherosclerosis is a progressive disease characterized by the accumulation of inflammatory cells, lipids, and connective tissue in the arteries. There are many evidences presenting that systemic inflammation in a low density takes place on the center of events causing plaque formation. Although in normal physiological conditions, the adhesion of leucocytes, starting plaque formation, to the endothelial cells lining vascular surfaces is impossible; in diseases coursing with inflammation such as COPD or asthma, the adhesion molecules appearing in endothelium enable the leucocytes to attach these surfaces. Some molecules such as CRP may cause progression and augmentation of these processes. Owing to this reason, blood CRP levels may give an idea about lung functions or vascular diseases. Moreover, increased atherosclerosis in COPD is a factor enhancing peripheral resistance in the vessels.

Chronic obstructive pulmonary disease is defined as a disease state characterized by progressive airflow limitation because of decreased lung elasticity and increased cholinergic vagal bronchoconstrictive tone. Bronchodilator therapy recovers airflow limitations by producing airway smooth-muscle relaxation. Anticholinergic agents inhibit tonic and phasic cholinergic activity and permit airways to dilate, whereas β_2 -agonists induce bronchodilation through stimulation of β_2 -receptors, leading to an increase in cyclic adenosine monophosphate. Turaçlı et al.²³ showed the effect of phosphodiesterase enzyme inhibitors on retinal blood flow. They used systemic theophylline ethylenediamine in conjunction with

betaxolol to improve the effects of betaxolol on the aqueous humor dynamics of 42 primary open-angle glaucoma patients whose mean tonometric and tonographic results were below the expected values. After theophylline infusion, there was a significant increase in mean flow velocities of the retinal artery. Although phosphodiesterase enzyme inhibitors were shown to affect the blood flow in orbital vessels, there is no report in the literature about the effects of anticholinergic agents and β_2 -agonists on orbital circulation. Our COPD and some asthma patients were taking phosphodiesterase enzyme inhibitor treatments that might also increase the orbital blood flow.

In conclusion, retrobulbar hemodynamics detected by CDU became abnormal in COPD and asthma patients. A significant increase in PSV and EDV of the NPCAs, TPCAs, and CRAs might be attributed to both hypoxia and hypercapnia and also COPD and asthma treatments in those patients. The increase in the RI of these arteries reflects the increased vascular resistance or vasospasm that may be due to the effects of activated vascular mediators and/or atherosclerotic changes that are related to the systemic inflammation in COPD and asthma patients.

REFERENCES

1. Pesci A, Balbi B, Majori M, et al. Inflammatory cells and mediators in bronchial lavage of patients with chronic obstructive pulmonary disease. *Eur Respir J*. 1998;12:380–386.
2. Wouters EF, Creutzberg EC, Schols AM. Systemic effects in COPD. *Chest*. 2002;121(5):127–130.
3. Halvani A, Tahghighi F, Nadooshan HH. Evaluation of correlation between airway and serum inflammatory markers in asthmatic patients. *Lung India*. 2012;29(2):143–146.
4. Wouters EF, Reynaert NL, Dentener MA, et al. Systemic and local inflammation in asthma and chronic obstructive pulmonary disease: is there a connection? *Proc Am Thorac Soc*. 2009;6(8):638–647.
5. Bousquet J, Jeffery PK, Busse WW, et al. Asthma. From bronchoconstriction to airways inflammation and remodeling. *Am J Respir Crit Care Med*. 2000;161(5):1720–1745.
6. Tunc M, Arbak P, Balbay O, et al. Ocular complications in patients with severe COPD induced by cigarette smoking. *Türkiye Klinikleri J Ophthalmol*. 2003;12(4):200–203.
7. Luksch A, Garhofer G, Imhof A, et al. Effect of inhalation of different mixtures of O₂ and CO₂ on retinal blood flow. *Br J Ophthalmol*. 2002;86:1143–1147.
8. Ozer T, Altin R, Ugurbas SH, et al. Color Doppler evaluation of the ocular arterial flow changes in chronic obstructive pulmonary disease. *Eur J Radiol*. 2006;57:63–68.
9. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31(1):143–178.
10. Pauwels RA, Buist AS, Calverley PM, et al. GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med*. 2001;163:1256–1276.
11. Johnston AJ, Steiner LA, Gupta AK, et al. Cerebral oxygen vasoreactivity and cerebral tissue oxygen reactivity. *Br J Anaesth*. 2003;90:774–786.
12. Patterson Jr JL, Heyman A, Battey LL, et al. Threshold of response of the cerebral vessels of man to increase in blood carbon dioxide. *J Clin Invest*. 1955;34:1857–1864.

13. Maclay JD, McAllister DA, Mills NL, et al. Vascular dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;180(6):513–520.
14. Platt JF, Ellis JH, Rubin JM, et al. Intrarenal arterial Doppler sonography in patients with nonobstructive renal disease: correlation of resistive index with biopsy findings. *AJR Am J Roentgenol*. 1990;154:1223–1227.
15. Roland M, Bhowmik A, Sapsford RJ, et al. Sputum and plasma endothelin-1 levels in exacerbations of chronic obstructive pulmonary disease. *Thorax*. 2001;56:30–35.
16. Sofia M, Mormile M, Faraone S, et al. Increased 24-h endothelin-1 urinary excretion in patients with chronic obstructive pulmonary disease. *Respiration*. 1994;61:263–268.
17. Zietkowski Z, Skiepkowski R, Tomasiak MM, et al. Endothelin-1 in exhaled breath condensate of allergic asthma patients with exercise-induced bronchoconstriction. *Respir Res*. 2007;8:76.
18. Gawlik R, Jastrzebski D, Ziora D, et al. Concentration of endothelin in plasma and BALF fluid from asthmatic patients. *J Physiol Pharmacol*. 2006;57Suppl 4:103–110.
19. Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vaso-constrictor peptide produced by vascular endothelial cells. *Nature*. 1988;332:411–415.
20. Polak K, Luksch A, Frank B, et al. Regulation of human retinal blood flow by endothelin-1. In: *Exp Eye Res*. 2003;76:633–640.
21. Sun WX, Jin D, Li Y, et al. Increased arterial stiffness in stable and severe asthma. *Respir Med*. 2014;108(1):57–62.
22. Weiler Z, Zeldin Y, Magen E, et al. Pulmonary function correlates with arterial stiffness in asthmatic patients. *Respir Med*. 2010;104(2):197–203.
23. Turacı ME, Tamer C, Celenk MK, et al. Additive effect of systemic phosphodiesterase inhibitor on betaxolol in primary open angle glaucoma. *Türkiye Klinikleri J Ophthalmol*. 1995;4(4):340–344.