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## Pertseva TO

Dnipropetrovsk Medical  
Academy of Health Ministry of  
Ukraine, Department of Internal  
Medicine 1, Ukraine,  
Dnipropetrovsk, 49000, 13,  
Batumskaya str.

## Konopkina LI

Dnipropetrovsk Medical  
Academy of Health Ministry of  
Ukraine, Department of Internal  
Medicine 1, Ukraine,  
Dnipropetrovsk, 49000, 13,  
Batumskaya str.

## Yakovleva VH

Dnipropetrovsk Medical  
Academy of Health Ministry of  
Ukraine, Department of Internal  
Medicine 1, Ukraine,  
Dnipropetrovsk, 49000, 13,  
Batumskaya str.

## Correspondence:

### Yakovleva VH

Dnipropetrovsk Medical  
Academy of Health Ministry of  
Ukraine, Department of Internal  
Medicine 1, Ukraine,  
Dnipropetrovsk, 49000, 13,  
Batumskaya str.

## Effects of Two-Component Standard Treatment of Chronic Obstructive Pulmonary Disease on Platelet-Vessel Wall Interaction Component and Coagulation Component of Hemostasis

Pertseva TO, Konopkina LI, Yakovleva VH

### Abstract

There is a correlation between the severity of clinical symptoms and ventilation disorders in chronic obstructive pulmonary disease (COPD) patients and degree of blood coagulation system disorders. Patients with severe bronchial obstruction form the most challenging category in terms of disease prognosis. Some reports state that impaired haemostasis in COPD patients can be corrected with both anti-inflammatory agents and bronchodilators. However, the effects of medications commonly administered to treat COPD on haemostasis remain understudied.

**Aim:** to evaluate the effects of adequate two-component standard treatment on platelet-vessel wall interaction and coagulation status of patients with severe COPD in view of severity of systemic inflammation.

**Materials and methods.** We have examined 30 patients with severe COPD ( $FEV_1 < 50\%$  pred.) in a stable phase. Prior to inclusion in the study, patients did not receive any adequate therapy with inhaled glucocorticosteroids (IGCS) or long-acting bronchodilators, or a combination thereof. All patients were screened twice – at baseline and two months after assignment of adequate standard therapy. Patients' complaints and disease history were carefully reviewed, objective data were collected, and functional and blood tests to assess hemorheology status and severity of systemic inflammatory were performed at baseline (Visit 1). COPD treatment was corrected for all patients during this visit: two-component therapy with salmeterol and fluticasone propionate in a fixed combination. After two months (Visit 2), in addition to re-evaluation of clinical symptoms, pulmonary ventilation function was measured, laboratory tests were performed and therapy compliance was assessed for all patients.

**Results.** Since there no adequate standard treatment is available for COPD patients disorders develop in both platelet-vessel wall interaction and coagulation parts of haemostasis. Use of two-component standard treatment for two months helps stabilise the extrinsic pathway of the coagulation cascade, reduce platelet adhesion activity and decrease systemic inflammation, and has no effect on other parameters of the coagulation component of haemostasis.

**Conclusion.** Adequate standard treatment of patients with severe COPD helps stabilise disorders of the coagulation part of haemostasis in the extrinsic coagulation pathway and causes no effects on the platelet-vessel wall interaction component of haemostasis.

**Keywords:** chronic obstructive pulmonary disease, haemostasis, coagulation, platelet adhesion.

### Introduction

It is currently known that patients with chronic obstructive pulmonary disease (COPD) respond to hypoxia by developing compensatory stimulation of erythropoiesis, hypercapnia, hypokalemia or respiratory acidosis [6, 11, 14]. These disorders can increase the activity of coagulation factors [18, 19]. On the other hand, data show that increased production of proinflammatory cytokines in COPD patients can cause the destruction of the endothelial tissue of blood vessels. It also contributes to abnormal hemorheology status [15, 17, 18, 19] of both platelet-vessel wall interaction [7, 13] and coagulation [3, 12] components.

Clinical study results demonstrate that there is a close correlation between the severity of clinical symptoms/ventilation disorders in COPD patients and degree of blood coagulation system disorders [3, 12, 16, 17]. It means that COPD patients, especially those with severely impaired pulmonary ventilation function (PVF) and a number of symptoms, need special care from clinicians so that risks of haemostasis disorders can be identified and for timely preventive therapy [8, 16].

There are recent data in scientific literature indicating that abnormal haemostasis in COPD patients can be corrected with both anti-inflammatory agents [1, 3, 4] and bronchodilators [5].

Commonly administered by such patients. V. K. Havrysyuk *et al.* [1] showed that platelet aggregation activity significantly reduced after just one day of fenspiride hydrochloride dosing in COPD patients, while the studies conducted by D. V. Dobryanskyi [3] demonstrated that three-week treatment with fenspiride hydrochloride also had a positive effect on rheological properties of blood. M. M. Yehorova [5] suggests that use of tiotropium bromide in COPD patients causes bronchodilation and can also enhance coagulation properties of blood improving overall hemorheology profile.

However, the mechanisms of disorders of the platelet-vessel wall interaction and coagulation elements of haemostasis in COPD patients as well as the levels at which those disorders occur still remain understudied and effects of medications commonly administered to treat bronchial obstruction are poorly explored.

In view of the aforesaid and taking into account that patients with severe bronchial obstruction form the most challenging category in terms of disease prognosis, the aim of our study was to evaluate the effects of two-component adequate standard treatment (Seretide® Discus® combination therapy) on platelet-vessel wall interaction and coagulation status of patients with severe COPD in view of severity of systemic inflammation.

### Materials and methods

We have examined 30 patients with severe COPD (all patients had stage III or IV disease and were classified as category C and category D patients) in a stable pathological process phase (25 (83.3%) men and 5 (16.7%) women; mean age was 65.4±7.9 years) who formed the main group. All patients had a history of active smoking or were active smokers at screening (with a pack/year factor 38.1±14.7). Prior to inclusion in the study, patients did not receive any adequate therapy with inhaled glucocorticosteroids (IGCS) or long-acting bronchodilators, or a combination thereof (or did not take those medications, or were not taking them on a regular basis, or were taking them in inadequate doses). During at last two last months, patients were receiving a combination drug containing short-acting bronchodilators (fenoterol, a short-acting  $\beta_2$ -agonist, and ipratropium bromide, a short-acting anticholinergic drug) in 4 to 8 inhalation doses daily, and, where necessary, salbutamol (200  $\mu$ g dose).

All patients gave their written informed consent to participate in the study.

COPD was diagnosed pursuant to Order No.555 of the Ministry of Health of Ukraine dated June 27, 2013 [9]. Patients a history of and current severe cardiovascular disorders at screening, a history of severe heart failure, thromboembolism associated with venous insufficiency of the lower extremities, a history of and current cancer at screening, or obesity were excluded from the study.

All patients were screened twice – at baseline and two months after assignment of adequate standard therapy.

Patients' complaints and disease history were carefully reviewed, objective data were collected, and functional and laboratory tests were performed at baseline (Visit 1). COPD treatment was corrected for all patients during this visit: two-component therapy with a long-acting  $\beta_2$ -agonist (salmeterol) and an inhaled corticosteroid (IGCS) (fluticasone propionat) in a fixed combination (Seretide® Discus® 50/500  $\mu$ g, 1 inhalation dose BID) and, where necessary, salbutamol (200  $\mu$ g dose). All patients were also instructed about the need to take adequate therapy, received recommendations for daily

monitoring of clinical symptoms, and all possible side effects of the drug components were explained.

After two months (Visit 2), in addition to re-evaluation of clinical symptoms, PVF was measured, blood tests to assess hemorheology status were performed and therapy compliance was assessed for all patients. Therapy compliance was measured by the number of Seretide® Discus® doses taken over two months as percentage of the drug amount which was supposed to be administered over that period. Compliance was considered sufficient if the value was between 80% and 120%, and insufficient if the value was beyond those limits.

The control group for haemostasis assessment included 19 virtually healthy individuals comparable with COPD patients by age and sex (mean age was 54.4±3.4 years; 15 men (78.9%) and 4 women (21.1%)). Participants in the examined control group also had a history of active smoking or were active smokers at screening (with a pack/year factor 35.2±13.8).

Cough expression and sputum quantity were measured by using V. M. Savchenko's method [10], cough severity — with a 5-point scale (where 0 means no cough; 1 — rare, insignificant cough; 2 — frequent but not activity-limiting cough; 3 — frequent, activity-limiting cough; 4 — cough that attracts attention for most part of the day); sputum quantity — with a 5-point scale (where 0 means no sputum; 1 — insignificant amount; 2 — moderate amount; 3 — much; 4 — very much). To assess dyspnoea severity we used the modified British Medical Research Council (mMRC) scale recommended for COPD patients and containing 5 grades of dyspnoea.

The global effects of the disease on patient's daily life were measured with the 8-items COPD Assessment Test (CAT) with possible total score from 0 to 40. [9].

PVF was assessed with a morning fasting computer-based spirometry study by using Master Screen Body/Diff system (Jager, Germany). Levels of forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) as percentage of the predicted value as well as the FEV<sub>1</sub>/FVC ratio were calculated. Reversibility of bronchial obstruction was measured by the change in FEV<sub>1</sub> absolute value (mL) after inhalation of 400  $\mu$ g of a short-acting  $\beta_2$ -agonist (salbutamol).

To assess the status of the extrinsic coagulation pathway of haemostasis we used prothrombin index (PI) which, if increased, indicates disorders of coagulation properties of the blood towards hypercoagulability; prothrombin ratio (PR) and international normalised ratio (INR), one of the key parameters of the state of the coagulation system and a standard factor of coagulation efficiency of the blood clotting system.

For the intrinsic and common pathways of the coagulation cascade we assessed the activated partial Thromboplastin time (aPTT), a versatile measure of deficit of all coagulation factors.

To assess procoagulant activity in haemostasis we measured thrombin time (PT), a reduced value of which is a marker of abnormal fibrinogen to fibrin transformation and increased tendency to hypercoagulability, and fibrinogen (Fg) levels (g/L), the only factor of the coagulation system and an acute-phase protein of inflammation.

Anticoagulation system was assessed by measuring the levels of antithrombin III (AT III), the most important cofactor of anticoagulation mechanisms.

The platelet-vessel wall interaction component of haemostasis was assessed by calculating the modified platelet adhesiveness (retention) index (PAI) (with glass beads). PAI was calculated by using the following equation: adhesiveness index (%) =

(number of pre-column platelets in blood – number of post-column platelets in blood)/(number of pre-column platelets in blood) x 100%. Elevated PAI indicates the presence of haemostasis disorders in the platelet-vessel wall interaction component towards hypercoagulability.

Plasma C-reactive protein (CRP) (mg/L) was measured as a systemic inflammation marker by immunoturbidimetric technique [17].

Statistical analysis of the results was performed by using biometric methods of analysis implemented in EXCEL-2003 and STATISTICA 6.0 software packages [8, 12]. Significance of differences in mean values for unrelated samples was evaluated by using the Student’s t-test and Mann-Whitney U test, for related samples by the Wilcoxon signed-rank test and Student’s t-test for dependent groups. The difference between comparable values was considered reliable at  $p < 0.05$ .

**Results and discussion**

During Visit 1, all patients were screened according to the plan and clinical diagnosis of severe COPD was verified for all patients. The results were processed for statistics purposes. However, though all patients were instructed at Visit 1 about the need for using adequate COPD therapy, at Visit 2 it was found out that approximately half (14 (46.7%)) of patients had poor therapy compliance: 10 (71.4%) of them for economic

reasons (could not buy the drugs) and 4 (28.6%) due to personal fear of taking glucocorticoids. Laboratory tests were not performed for those patients at Visit 2. Patients who demonstrated sufficient therapy compliance (16 (53.3%), 12 (75.0%) men and 4 (25.0%) women; mean age was  $68.1 \pm 6.4$  years; pack/year factor was  $32.6 \pm 17.1$ ) formed subgroup 1 of the main group and had a full examination at Visit 2.

Comparative statistical analysis was performed for the overall values of subgroup 1 of the main group measured at Visit 1, and for the values of subgroup 1 obtained at Visit 1 and Visit 2. The clinical parameters of patients in the main group and subgroup 1 did not show any significant difference (Table 1). It means that subgroup 1 was representative by its clinical parameters.

The analysis showed that at the time of Visit 1 all patients in subgroup 1, just as patients in the main group, had a great number of symptoms (>10 points by the CAT test). Two months later (Visit 2), improvement in daily activities and general health, as measured by the CAT test, and in individual clinical signs of the disease compared to baseline were seen in association with adequate administration of Seretide® Discus®. The clinical parameter levels in Table 1 are represented for convenience as the arithmetic mean (M) and error of mean (m).

**Table 1:** Clinical Parameter Levels in COPD Patients by Treatment Stages

Study Group	Values (M±m)			
	CAT (score)	mMRC (score)	cough (score)	sputum (score)
Main group (n=30):	16.50±1.16	2.17±0.15	1.23±0.11	1.40±0.14
Subgroup 1 (n=16):				
at Visit 1	16.81±1.77	2.31±0.24	1.19±0.16	1.38±0.22
at Visit 2	14.56±1.52	1.63±0.13	0.81±0.10	0.50±0.13
p	$p_m-p_1 > 0.05$ $p_1-p_2 < 0.05$	$p_m-p_1 > 0.05$ $p_1-p_2 < 0.05$	$p_m-p_1 > 0.05$ $p_1-p_2 < 0.05$	$p_m-p_1 > 0.05$ $p_1-p_2 < 0.05$

Note:

- 1. m— main group;
- 2. 1— subgroup 1 at Visit 1;
- 3. 2— subgroup 1 at Visit 2.

PVF levels in patients of the main group and subgroup 1 did not show any significant difference (Table 2). This means that subgroup 1 was representative by PVF levels.

FEV<sub>1</sub> and FVC levels in patients from subgroup 1 at Visit 2 did not differ significantly from those levels at Visit 1 ( $p > 0.05$ ), though an increase in the FEV<sub>1</sub>/FVC ratio compared to baseline was noted ( $p < 0.05$ ).

**Table 2:** PVF Levels in COPD Patients by Treatment Stages

Study Group	Parameters (Med [25–75%])		
	FEV <sub>1</sub> (% pred.)	FVC (% pred.)	FEV <sub>1</sub> /FVC
Main group (n=30):	44.2 [33.5–46.1]	84.1 [75.6–88.5]	0.38 [0.33–0.49]
Subgroup 1 (n=16):			
at Visit 1	39.9 [31.6–45.1]	88.1 [75.3–95.7]	0.35 [0.32–0.39]
at Visit 2	42.0 [35.7–46.4]	87.5 [82.3–92.2]	0.38 [0.34–0.46]
p	$p_m-p_1 > 0.05$ $p_1-p_2 > 0.05$	$p_m-p_1 > 0.05$ $p_1-p_2 > 0.05$	$p_m-p_1 > 0.05$ $p_1-p_2 < 0.05$

Note: please see Table 1.

The analysis showed that the levels of the platelet-vessel wall interaction and coagulation elements of haemostasis in patients from the main group and subgroup 1 did not have any significant difference. Therefore, subgroup 1 was representative by the key haemostasis parameters.

Prothrombin complex (PI, PR, INR) levels in patients of the main group at Visit 1, just as in patients from subgroup 1, were significantly different from those levels in the control group and were indicative of disorders in the coagulation component of haemostasis towards hypercoagulability (Table 3).

Though the analysis of the coagulation element of haemostasis in patients from subgroup 1 showed that PI, PR and INR levels at Visit 2 and 2 months after therapy correction were different from those in the control group with a tendency towards hypercoagulability, it was determined that during Seretide® Discus® treatment PI level decreased significantly while PR and INR levels increased compared to baseline. These changes suggest that there is a positive effect of the two-component therapy on the extrinsic coagulation pathway parameters.

**Table 3:** Extrinsic Coagulation Pathway Parameters in COPD Patients

Study Group	Parameters (Med [25–75%])		
	PI (%)	PR	INR
Main group (n=30):	109.0 [108.0–112.0]	0.92 [0.89–0.93]	0.90 [0.86–0.91]
Subgroup 1 (n=16):			
at Visit 1	111.5 [109.0–117.0]	0.89 [0.85–45.1]	0.87 [0.82–0.90]
at Visit 2	103.0 [100.5–112.5]	0.97 [0.89–0.99]	0.96 [0.87–0.99]
Control group (n=19)	97.0 [23.4– 28.2]	1.03 [1.0–1.05]	1.04 [1.0–1.06]
p	p <sub>m</sub> -p <sub>c</sub> <0.05 p <sub>m</sub> -p <sub>1</sub> >0.05 p <sub>1</sub> -p <sub>c</sub> <0.05 p <sub>2</sub> -p <sub>c</sub> <0.05 p <sub>1</sub> -p <sub>2</sub> <0.05	p <sub>m</sub> -p <sub>c</sub> <0.05 p <sub>m</sub> -p <sub>1</sub> >0.05 p <sub>1</sub> -p <sub>c</sub> <0.05 p <sub>2</sub> -p <sub>c</sub> <0.05 p <sub>1</sub> -p <sub>2</sub> <0.05	p <sub>m</sub> -p <sub>c</sub> <0.05 p <sub>m</sub> -p <sub>1</sub> >0.05 p <sub>1</sub> -p <sub>c</sub> <0.05 p <sub>2</sub> -p <sub>c</sub> <0.05 p <sub>1</sub> -p <sub>2</sub> <0.05

Note:

1. 1 — subgroup 1 at Visit 1;
2. 2 — subgroup 1 at Visit 2;
3. m — main group;
4. c — control group.

aPTT levels in both the main group of patients at visit 1 and subgroup 1 were significantly lower than those identified in control group (p<0.05) (Table 4). aPTT levels in subgroup 1 after two months of treatment with Seretide® Discus® did not significantly change compared to baseline (p>0.05) and was significantly lower in the control group (p<0.05) which is indicative of abnormal coagulation haemostasis towards hypercoagulability and lack of effects of the two-component therapy on those disorders.

As regards the procoagulant activity of haemostasis, PT and Fg levels in patients of the main group and subgroup 1 at Visit 1 were not significantly different from those in the control group. Following the correction therapy (at Visit 2), PT and Fg levels in subgroup 1 were identical to Visit 1 levels and did not show any significant difference with the control group. The assigned therapy had no significant effect on the two last parameters. No changes in PT, that characterises the common pathway of the coagulation cascade, and changes in aPTT levels towards hypercoagulability all show that there are haemostasis disorders mainly in the intrinsic pathway of the coagulation cascade in patients with severe COPD.

**Table 4:** Parameters of Intrinsic and Common Pathways of Coagulation Cascade in COPD Patients

0	Parameters (Med [25–75%])		
	aPTT (s)	PT (s)	Fg (g/L)
Main group (n=30):	22.2 [18.2–24.0]	16.3 [15.3–16.8]	3.5 [3.1–4.0]
Subgroup 1 (n=16):			
at Visit 1	22.5 [18.6–23.8]	16.0 [15.3–16.7]	3.5 [3.2–3.9]
at Visit 2	22.2 [21.0–23.4]	15.5 [15.8–17.2]	3.5 [2.7–4.4]
Control group (n=19)	26.4 [23.4–28.2]	16.5 [15.7–17.6]	3.1 [2.6–3.5]
p	p <sub>m</sub> -p <sub>c</sub> <0.05 p <sub>m</sub> -p <sub>1</sub> >0.05 p <sub>1</sub> -p <sub>c</sub> <0.05 p <sub>2</sub> -p <sub>c</sub> <0.05 p <sub>1</sub> -p <sub>2</sub> >0.05	p <sub>m</sub> -p <sub>c</sub> >0.05 p <sub>m</sub> -p <sub>1</sub> >0.05 p <sub>1</sub> -p <sub>c</sub> >0.05 p <sub>2</sub> -p <sub>c</sub> >0.05 p <sub>1</sub> -p <sub>2</sub> >0.05	p <sub>m</sub> -p <sub>c</sub> >0.05 p <sub>m</sub> -p <sub>1</sub> >0.05 p <sub>1</sub> -p <sub>c</sub> >0.05 p <sub>2</sub> -p <sub>c</sub> >0.05 p <sub>1</sub> -p <sub>2</sub> >0.05

Note: please see Table 3.

It should be noted that AT III levels in patients of the main group (96.0 [82.0–107.0]%) were not significantly different

from those in the control group. In subgroup 1, this value both before and after therapy correction (Visit 2) (87.5 [77.5–103.5] and 88.0 [84.0–101.0]%, respectively) was lower than in the control group (103.0 [98.0–106.0]%), which means that examined patients have an increased tendency to hypercoagulability. Therefore, a two-month course of Seretide® Discus® treatment had an insignificant effect on this value. These changes are indicative of both zero response from the anticoagulation blood system to coagulation disorders in COPD patients of the main group and inhibition of the fibrinolytic blood system in patients of subgroup 1, which was reported in the literature [2, 8].

The change in the coagulation component of haemostasis means that COPD patients are predisposed to hypercoagulability. Unless the disease is adequately treated, abnormalities develop in both the extrinsic and intrinsic coagulation pathways. However, even a two-month course of a two-component therapy with Seretide® Discus® contributes to stabilisation of haemostasis disorders in such patients to some extent.

As for the platelet-vessel wall interaction component of haemostasis, the PAI levels in patients of the main group at Visit 1, just as in patients of subgroup 1 (45.5 [37.0–53.0] and 37.0 [33.5–43.5]%, respectively) were significantly higher than in the control group (27.0 [22.0–33.0]%) (p<0.05). After two months of Seretide® Discus® treatment, the levels in subgroup 1 (35.0 [27.0–44.0]%) decreased significantly compared to baseline (p<0.05) and was identical to the value obtained for the control group (p<0.05). Such PAI levels mean that the two-component treatment had a positive effect on the adhesive activity of platelets.

CRP levels at Visit 1 in both patients of the main group and subgroup 1 (5.59 [5.1–7.4] and 6.1 [5.7–9.7] mg/L, respectively) were significantly higher than in the control group (3.2 [3.6–3.8] mg/L) (p<0.05), which demonstrates the severity of the systemic inflammatory response in COPD patients. CRP levels in patients of the main group and subgroup 1 did not show any significant difference. Therefore, subgroup 1 was representative by this value.

Though CRP in patients of subgroup 1 both at Visit 2 (5.2 [4.7–6.8] mg/L), respectively) was significantly higher than in the control group (p<0.05), after two months of treatment with Seretide® Discus® the levels decreased significantly compared to baseline (p<0.05) and approximated the levels of the control group, please see Fig. 1.

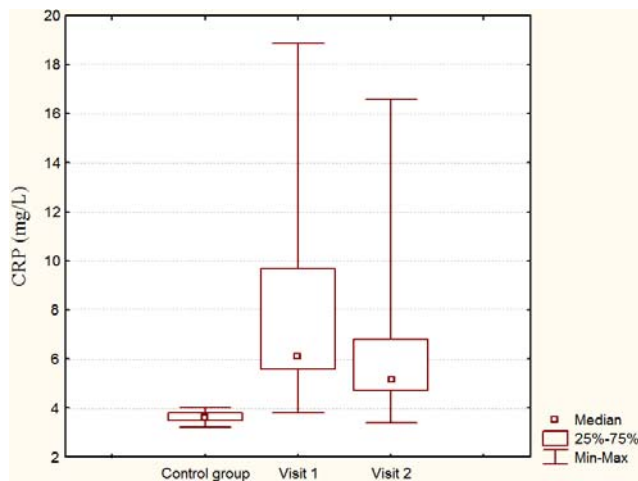


Fig. 1: CRP levels in patients with severe COPD by treatment stages.

Our data indicate that an adequate two-component standard treatment of patients with severe COPD may decrease the severity of systemic inflammatory response and, therefore, may help normalise the coagulation element of haemostasis. A search for new methods to correct of haemostasis in COPD patients, especially in those with severe and distinct clinical symptoms, is a promising area of the future research.

### Conclusions

1. Haemostasis disorders develop in both platelet-vessel wall interaction and coagulation parts of haemostasis of severe COPD patients since there no adequate standard treatment is available for them.
2. An adequate standard treatment of patients with severe COPD helps stabilise disorders of the coagulation part of their haemostasis in the extrinsic coagulation pathway.
3. An adequate standard treatment of patients with severe COPD has a positive effect on platelet adhesion activity and helps stabilise the platelet-vessel wall interaction component of haemostasis.

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