

Research Article

Study of Prothrombotic Markers in COPD

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A B S T R A C T

Background: Chronic Obstructive Pulmonary Disease (COPD) is chronic inflammatory condition that is known to be a prothrombotic state.

Objective: To study the prothrombotic markers and coagulation profile in patients of Stable COPD and during its exacerbation and to compare these parameters in stable phase of disease and during exacerbation.

Materials and Method: A cross sectional study in which 30 patients of COPD with exacerbation and 30 patients with stable COPD were recruited. Patients having acquired thrombotic risk factors like diabetes, hypertension, coronary artery disease, chronic kidney disease, chronic liver disease, malignancy & sepsis or any immunocompromised condition along with those who were on anticoagulant therapy, statins or antihypertensive medications were excluded from the study. Levels of prothrombotic markers (von Willebrand Factor antigen, D-dimer, fibrogen) and Caogulation profile (Prothrombin time and activated Partial Thromboplastin Time) were estimated in both the groups and repeated after stabilization of exacerbation phase also. There parameters were then statistically analyzed.

Observation and Results: A generalized prothrombotic state was observed in exacerbation phase of COPD as compared to stable phase of COPD. Furthermore, all the parameters including fibrinogen, vWF, PT and aPTT showed persistent declining trend from exacerbation towards stabilization.

Conclusion: COPD with acute exacerbation is a state of augmented prothrombotic state. On stabilization of acute exacerbation with treatment, coagulation profile came to a level lower than that of patients in stable phase of COPD. In exacerbation phase of COPD vWF values were significantly elevated than in stable phase.

Keywords: COPD, Prothrombotic Markers, Fibrinogen, Von Willebrand Factor, Acute Exacerbation of COPD

Introduction

Chronic Obstructive Pulmonary Disease (COPD), a very common disease involving partial reversibility of airflow limitation, has at its core the continuing inflammation of respiratory system as well as at systemic level.¹ Various extra pulmonary or systemic effects of COPD can be attributed to this persistent inflammatory state.² Exacerbations, a part of natural disease process of COPD, represent amplification of this inflammatory response which is associated with increased concentrations of certain inflammatory mediators i.e., TNF- α , LT β -4 & IL-8, etc.

Increased pulse wave velocity, a surrogate marker for central arterial stiffness, endothelial dysfunction & atherosclerosis correlate with reduced FEV₁.³ This consequently leads to crowning of CAD as one of the leading cause of death in COPD patients.⁴ Looking forward the association of COPD & atherothrombosis, four pathological factors are major contributors: chronic systemic inflammation, hypercoagulable state, platelet activation & oxidative stress.⁵ The persistent inflammatory state can trigger coagulation by promoting tissue-factor gene expression in endothelial cells.⁶ Hypoxia also could either reduce endothelial thrombomodulin expression or activate factor X.⁷ Serum fibrinogen level also rises during COPD exacerbation.⁸ Platelet aggregability, as assessed in vivo by measuring 11-dehydro-thromboxane- β -2, the urinary metabolite of (TXA2) also shows elevated levels in hypoxemic COPD patients.⁹ Hydrogen peroxide in exhaled breath condensate, a marker of oxidative stress in lungs, has been found to be persistently elevated in COPD patients.¹⁰

Endothelial dysfunction, as characterized by increased levels of CRP, sICAM-1, IL-6, TNF- α , endothelin-1, complement & leptin as associated with COPD & its exacerbation.¹¹⁻¹³ Markers of hypercoagulation, Thrombin-Antithrombin III complex (TAT), fibrinopeptide A, & plasminogen activator inhibitor type 1 (PAI-1) had shown definite correlation with COPD exacerbation.¹⁴ Prothrombin time (PT), activated Partial Thromboplastin Time (aPTT) and von Willebrand Factor (VWF) are sensitive parameters of underlying hypercoagulable state. Fibrinogen is a marker of inflammation & D-dimer is a marker of secondary fibrinolysis following thrombosis.¹⁵ These parameters, therefore, can be used as markers of procoagulant state in patients of COPD & its exacerbation. We did this study targeting the same.

Methods

It was an observational cross-sectional study which was carried out in the Department of Medicine, Maulana Azad Medical College, New Delhi after approval from institutional ethics committee. Study subjects were 30 in-hospital patients of COPD with acute exacerbation and 30 stable

patients of diagnosed COPD (As per GOLD 2016) Patients having acquired thrombotic risk factors like diabetes, hypertension, coronary artery disease, chronic kidney disease, chronic liver disease, malignancy & sepsis or any immunocompromised condition were excluded from the study. Also, patients who were on anticoagulant therapy, statins or antihypertensive medications were excluded. The recruited patients were subjected to detailed history, physical examination and severity assessment (based on spirometry using portable spirometer- spirolab II). All the patients were prescribed a standard treatment regimen for COPD management. Those in exacerbation were admitted for proper treatment and discharged after a minimum of 5 days of inpatient care in hospital.

Blood samples were drawn on two different occasions – On day 1 of admission & on day 5 or later when the patients were clinically stable. For stable COPD patients only one sample was taken. Venous blood was collected into 3.8% trisodium citrate tubes for assessment of PT, aPTT, vWF, fibrinogen and D-dimer. In this study, we considered P-value of <0.05 as statistically significant.

Results and Observations

Thirty patients each of COPD with acute exacerbation and stable COPD were enrolled in the study. Amidst the uniform distribution of study subjects in various age groups, most patients were in the age group of 41-70 years corresponding to the peak age group of COPD population. 5% fell into 31-40 years, 30% in 41-50 years, 28.3% in 51-60 years, 25% in 61-70 years & 11.7% in >70 years age group. In this study, 47 patients were males & 13 were females. The mean BMI of all patients was 25 \pm 5.3. 33% of patients were having their BMI <23.5 kg/m².

After categorizing the patients based on severity of COPD using GOLD 2016, 4 patients were in GOLD stage II (moderate), 30 patients were in GOLD stage III (severe) & 26 patients were in GOLD stage IV (very severe). Amongst the exacerbation group, patients fell equally into stage III & IV. All patients were smokers with a smoking mean of 25 \pm 5.9 pack years.

Analysis of Coagulation Parameters and Prothrombotic Markers

All the parameters like PT, aPTT, fibrinogen and vWF were obtained as quantitative values except D-dimer which was measured qualitatively and expressed as positive or negative. In COPD exacerbation group, out of 30 patients, 20 had negative and 10 had positive D-dimer value. Out of these 10 patients only 4 patients remained positive on follow up after minimum of 5 days of inpatient stabilization. On the other hand, only 5 patients out of thirty had positive result in stable COPD group.

Table 1. Prothrombotic Markers in different stages of COPD at the time of exacerbation

Prothrombotic Markers	GOLD status	N	Mean \pm S.D.	p-value
PT	Severe	15	1.1010 \pm 0.7539	0.08
	Very severe	15	1.1741 \pm 0.1375	
aPTT	Severe	15	1.1208 \pm 0.1804	0.57
	Very severe	15	1.1679 \pm 0.2643	
vWF	Severe	15	147.45 \pm 14.23	0.96
	Very severe	15	147.70 \pm 16.61	
Fibrinogen	Severe	15	373.08 \pm 152.63	0.002
	Very severe	15	609.10 \pm 228.58	

Table 2. Comparison between COPD exacerbation and Post stabilisation

Prothrombotic markers	COPD exacerbation	Post Stabilisation	p-value
PT	1.13 (1.09-1.18)	1.02(1.00-1.03)	0.011
aPTT	1.14 (1.06-1.22)	1.03(1.01-1.05)	0.027
vWF	147.58 (141.90-153.25)	80.71(73.95-88.7)	<0.001
Fibrinogen	491.09 (406.86-575.31)	267.45(233.93-300.97)	<0.001

Table 3. Comparison between Exacerbation and Stable COPD group

Prothrombotic markers	COPD exacerbation	Stable COPD	p-value
PT	1.13(1.09-1.18)	1.09(1.00-1.18)	0.51
aPTT	1.14(1.06-1.22)	1.14(1.07-1.20)	0.99
vWF	147.58(141.90-153.25)	128.95(117.07-140.83)	0.006
Fibrinogen	491.09(406.86-575.31)	426.86(373.08-480.63)	0.28

Table 4. Prothrombotic Markers in different stages of stable COPD patients

Prothrombotic Marker	GOLD stage	N	Mean \pm S.D.	P-value
PT	Moderate	4	1.04 \pm 0.56	0.565
	Severe	15	1.14 \pm 0.31	
	Very severe	11	1.04 \pm 0.09	
aPTT	Moderate	4	1.01 \pm 0.038	0.34
	Severe	15	1.16 \pm 0.221	
	Very severe	11	1.15 \pm 0.127	
vWF	Moderate	4	124.22 \pm 53.19	0.079
	Severe	15	117.90 \pm 28.91	
	Very severe	11	145.74 \pm 20.31	
Fibrinogen	Moderate	4	411.77 \pm 111.25	0.011
	Severe	15	359.86 \pm 82.16	
	Very severe	11	523.70 \pm 172.72	

In patients of COPD with acute exacerbation (N=30), stage wise distribution of prothrombotic markers (mean and

standard deviation) is shown in Table 1. While comparing mean values using analysis of variance (ANNOVA), it was

found to be statistically significant between stage III (severe) and IV (very severe) COPD for serum fibrinogen level only ($p=0.002$).

In COPD exacerbation group, the mean value of fibrinogen was 491 ± 225 mg%, PT was 1.13 ± 0.11 , aPTT was 1.14 ± 0.22 & vWF was $147\pm 15\%$. When COPD exacerbation patients were stabilized after a minimum of 5 days of inpatient care, the mean values of fibrinogen, PT, aPTT & vWF were 267 ± 33.52 mg%, 1.02 ± 0.02 , 1.03 ± 0.02 and $80.71\pm 6.76\%$ respectively (Table 2).

The values of PT, aPTT, vWF and fibrinogen were observed to be raised significantly as compared to these values after stabilization (day 5). This is in agreement with our hypothesis that COPD exacerbation is a prothrombotic state.

In stable COPD group (N=30), however, the mean value of fibrinogen was 426 ± 144 mg%, PT was 1.09 ± 0.22 , aPTT was 1.14 ± 0.17 & vWF was 128 ± 31.8 . When we compared

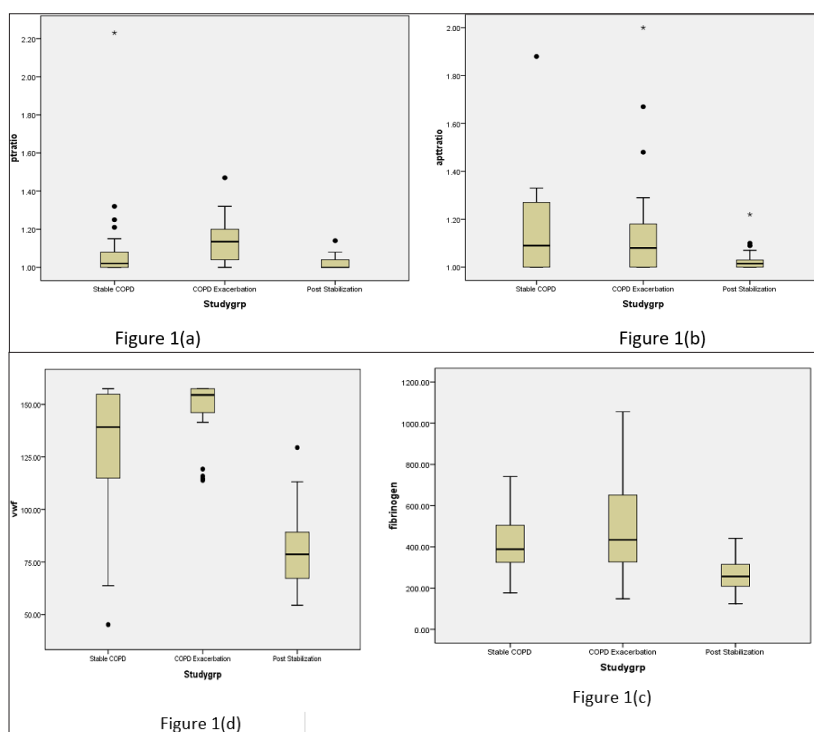
the values of coagulation parameters and prothrombotic markers between COPD exacerbation and stable COPD group patients enrolled in our study, only VWF was found to be significantly raised in exacerbation phase in comparison to the stable COPD group (Table 3). Although, the mean values of these parameters were much higher than the normal reference range even in these stable COPD patients.¹⁷

In patients of Stable COPD (N=30), stage wise distribution of prothrombotic markers (mean and standard deviation) is shown in Table 4. While comparing mean values using analysis of variance (ANNOVA), it was found to be statistically significant between stage III (severe) and IV (very severe) COPD for Serum fibrinogen level only.

A significant difference was seen in the mean values of aPTT, vWF antigen and fibrinogen levels while comparing parameters between stable COPD group and post stabilization (day 5) group, as shown in Table 5.

Table 5. Comparison between post stabilization and stable COPD patients' group

Prothrombotic markers	Stable COPD	Post stabilization	p-value
PT	1.0 (1.00-1.18)	1.02 (1.00-1.03)	0.162
aPTT	1.14 (1.07-1.20)	1.03 (1.01-1.05)	0.029
vWF	128.95 (117.07-140.83)	80.71 (73.95-88.7)	<0.001
Fibrinogen	426.86 (373.08-480.63)	267.45 (233.93-300.97)	0.001



Diagrammatic representation of various parameters among different group of patients are shown below in **Figure 1(a-d)** (using Box-whisker plot)

Figure 1(a-d). Box Whisker plot showing comparison of various parameters among different study groups. [a: PT, b: aPTT, c: vWF, d: Fibrinogen]

Discussion

This study was done to assess the prothrombotic state in COPD in various stages i.e., stable state, acute exacerbation and after its stabilization. There is paucity of data evaluating the relation between various stages of COPD with respect to various prothrombotic parameters like PT, aPTT, fibrinogen and vWF.

In our study, these parameters showed declining trends from exacerbation to post stabilization phase [PT ($p=0.001$) & aPTT ($p=0.027$)]. In this study, the mean value of vWF declined after stabilization as compared to exacerbatory phase (p -value <0.001). Also, stable COPD group had higher values than the normal reference range. In a recent study done by Mehmet Polati et al,¹⁵ vWF level was found to be the highest in acute exacerbation phase as compared to stable state, supporting our finding. Study conducted by Polosa et al showed 122% decline in vWF level from exacerbatory phase to the state of clinical stability.¹⁶

Fibrinogen, an acute phase reactant, plays a prominent role in clotting. The increase in its level, as it is associated with endothelial damage, has been found to be associated with the risk of cardiovascular disease.¹⁷ In our study also the mean value of fibrinogen showed a declining trend after stabilization as compared to exacerbatory state (p -value <0.001). Out of the parameters studied, fibrinogen was the only parameter which showed graded increase with increasing severity of COPD. This finding is similar to the finding of the meta analysis where there was graded increase in fibrinogen level with increase in severity of COPD.¹⁸ Mehmet Polati et al, however, found that microalbuminuria, vWF and fibrinogen all were helpful in grading the severity of COPD exacerbation.¹⁵

D-dimer, the specific degradation product of cross-linked fibrin, was measured qualitatively in our study. It can be used as a molecular marker of hypercoagulation and secondary increased fibrinolytic activity. In this study, 10 patients had positive D-dimer value which declined to 4 patients in post stabilization phase ($p=0.008$). These findings were also supported by other studies.¹⁹

This study provided evidence that acute exacerbation of COPD is associated with augmented prothrombotic state. The markers of coagulation such as PT, aPTT and markers of prothrombotic state: fibrinogen, D-dimer and vWF were significantly raised in acute exacerbation which subsequently decreased on stabilization. The systemic inflammation during COPD exacerbation may be the cause of this prothrombotic state. These markers were also raised significantly in stable COPD patients as compared to post stabilization value. However, patients of COPD with acute exacerbation post stabilization had lesser degree of procoagulants than stable COPD patients. This can be

explained by the fact that COPD is a chronic inflammatory disease in itself. Lesser degree of procoagulants in patients of COPD exacerbation post-stabilization might be attributable to the use of intravenous steroid therapy which decreases the systemic inflammation. While, in the stable COPD patients the systemic inflammation is ongoing and hence these markers had higher values than the normal population.

The elevated vWF, D-dimer and fibrinogen concentrations in the blood during acute exacerbation of COPD may precipitate thromboembolic events in these patients just as seen in ischemic heart disease.^{20,21} This is substantiated by deaths from pulmonary thromboembolism occurring in about 10% of patients admitted with acute exacerbation of COPD.²² The heightened procoagulant state during COPD exacerbation may predispose to venous thromboembolism and could, in principle, justify a general recommendation for anticoagulation and pharmacological thromboprophylaxis in these patients during exacerbation of their disease.

Present study has demonstrated the presence of hypercoagulable state in COPD patients. However, it has the limitation of small sample size. Further studies are needed to identify the exact mechanisms underlying the hypercoagulable state in COPD, and to determine whether anticoagulant therapy may be clinically useful in exacerbation of COPD. In our study, out of all parameters only vWF showed significant difference between exacerbation phase and stable phase of COPD ($p<0.006$). As the current study was not intended to prove vWF as a marker of exacerbation of COPD, further studies are required to clearly indicate whether vWF can be used as marker of acute exacerbation of COPD.

Conclusion

- COPD with acute exacerbation is a state of augmented prothrombotic state.
- On stabilization of acute exacerbation with treatment coagulation profile came to a level even lower than the patients in stable phase of COPD.
- vWF had been found to be significantly elevated in acute exacerbation phase of COPD than in stable phase.

Abbreviation

COPD: Chronic Obstructive Pulmonary Disease; PT: Prothrombin Time; PTT: Activated Partial Thromboplastin Time; VWF: Von Willebrand Factor; TNF: Tumour Necrosis Factor; LTs: Leukotrienes, Interleukins; CAD: Coronary Artery Disease; TX: Thromboxane; CRP: C-Reactive Protein; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Declaration

- **Ethics Approval:** This study was conducted only after approval from the institutional ethical committee

Maulana Azad Medical College and after obtaining informed consent from all the patient participants.

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Conflict of Interest: None

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