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Endothelial-coagulative activation during chronic obstructive pulmonary disease exacerbations

Patients with chronic obstructive pulmonary disease (COPD) are prone to clinical exacerbations of their disease and this is known to be associated with increased airway inflammation.[1] A prothrombotic condition resulting from the inflammatory activation of the endothelium may well occur during COPD exacerbations and could be a significant causative factor for pulmonary thromboembolism (PTE).[2] We tested the hypothesis that acute inflammatory responses of COPD exacerbation are associated with activation of the endothelial-coagulative system.

Surrogate markers of inflammation (IL-6), endothelium activation (von Willebrand Factor antigen – vWF:Ag), fibrinolytic activation (D-Dimer - D-D) and clotting stimulation (prothrombin fragment 1+2 - F1+2) were prospectively assayed in the blood of patients with COPD by commercial ELISA kits (IL-6, R&D Systems, Oxon, UK; Asserachrom vWF, Diagnostica Stago, Asnieres, France; Zymutest D-Dimer, Hyphen Biomed, Neuville-Sur-Oise, France; Enzygnost F1+2 Micro, Dade Behring, Marburg, Germany) at the time of hospital admission for acute exacerbation of their disease (visit 1), and after clinical resolution (visit 2). The diagnosis of COPD and the presence of disease exacerbation were documented during hospital admission based on current criteria. All patients were prescribed a standardized treatment regimen consisting of oral antibiotics, IV corticosteroids, nebulized bronchodilators and oxygen. Patients with commonly acquired thrombotic risk factors (e.g. hypertension, diabetes mellitus, malignancy, etc) were excluded. No patient received heparin, anticoagulants, statins or antihypertensive drugs during the study. All other treatment (including inhaled corticosteroids) remained constant throughout the study. The data obtained from the COPD patients were compared with that from control patients (with no diagnosis of COPD) who were hospitalized in the same institution for other respiratory conditions.

Complete datasets were available for 30 COPD patients and for 12 non-COPD controls for final analyses (*see summary data in Tables 1 and 2 in Supplementary Appendix*). At the time of exacerbation (visit 1), IL-6, vWF:Ag, D-D and F1+2 levels (mean±SEM) were elevated and decreased significantly when patients were clinically stable (visit 2) with IL-6 declining from 6.7±0.8 to 3.9±0.4 pg/mL ($p<0.001$; paired Student's *t*-test) (Figure 1A; left panel); vWF:Ag from 186.3±14.1 to 124.7±7.9% ($p<0.001$; paired Student's t-test) (Figure 1A; right panel); D-D from 232.1±30.0 to 129.5±7.4 ng/mL ($p<0.002$; paired Student's t-test)(Figure 1B; right panel); and F1+2 from 1.36±0.61 to 0.72±0.22 nmol/L ($p<0.001$; paired Student's t-test) (Figure 1B; left panel). A significant reduction in CRP levels from 32.5±6.0 to 2.3±0.4 mg/L ($p<0.001$; paired Student's *t*-test) was also reported. In the control group the levels of all the parameters studied were also elevated at admission (visit 1), but significant reductions were not observed at follow-up (visit 2) with the exception of D-D (*data not shown*).

This study shows that blood levels of vWF:Ag, D-D and F1+2 together with IL-6 are elevated in COPD patients during acute exacerbation of their disease, thus suggesting a relationship between acute inflammation, endothelial activation and clotting initiation. The present findings are in agreement with those of others. Earlier work by Wedzicha *et al*.[3] postulated an enhanced platelet activity in COPD by showing lower platelet aggregate ratio in hypoxemic COPD patients compared to controls with a trend to lesser aggregate ratios in the more hypoxemic patients. Further support for the view that a prothrombotic condition is present in COPD was provided by Alessandri *et al*.,[4] who demonstrated that about two-thirds of patients with stable COPD have elevated plasma levels of the thrombin generation marker prothrombin F1+2 fragment. This study also underlines the importance of systemic inflammation in COPD and it is in agreement with previous work showing that COPD patients have increased blood levels of fibrinogen and IL-6 during exacerbations of their disease.[5] Clinically, elevated vWF:Ag, D-D and F1+2 concentrations in blood have been reported to increase the likelihood of throboembolic events,[6] which are noted during acute exacerbations of COPD.

COPD exacerbations may be caused by severe pneumonia and this *per se* is likely to explain the underlying activation of the endothelial-coagulative system.[7,8]

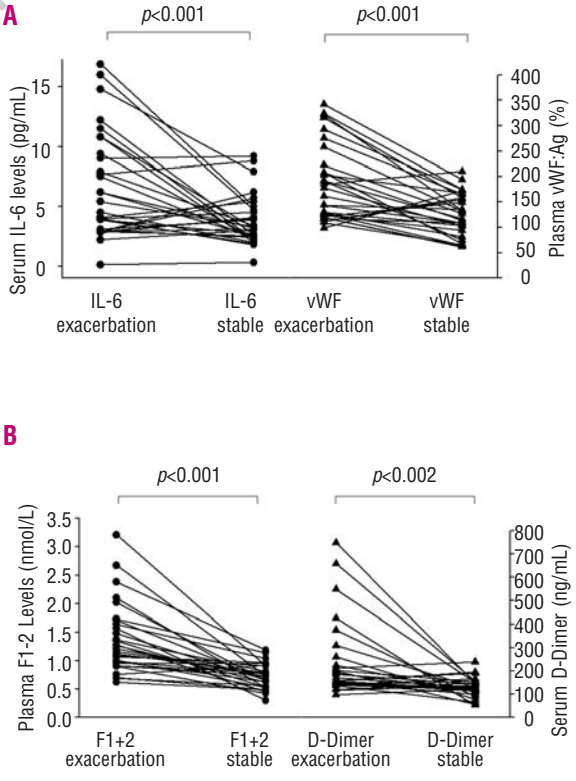

Figure 1. (A) Serum levels of IL-6 (pg/mL) and plasma vWF:Ag (%) in COPD subjects during exacerbation and in stable state. (B) Plasma levels of F1+F2 (nmol/L) and serum D-Dimer (ng/mL) in COPD subjects during exacerbation and in stable state.

However, increases in coagulation markers have not been reported in mild community acquired pneumonia.[9] Of note, upper airway infections (generally post viral) and poor treatment compliance are also common causes of COPD exacerbation,[1] and severe pneumonia is unlikely in our COPD patients given that specific signs of consolidation and diffuse infiltration were lacking on their chest X-rays and the absence of high grade fever. The lack of prothrombotic conditions in the control patients is probably due to the heterogeneous nature of their diseases, which included respiratory tract infections/mild pneumonia (n=3), asthma (n=4), pulmonary fibrosis (n=3), and obstructive sleep apnea syndrome (n=2).

Activation of the endothelial-coagulative system in the course of acute exacerbations in COPD may result in an increased risk of PTE and contribute to severity of symptoms. Death from PTE occurs in about 10% of patients admitted for an acute exacerbation of COPD.[10] The incidence of fatal PTE in acute exacerbation of COPD appears to be even higher when reported at post-mortem. Pulmonary emboli have been found in up to 30% of patients who died from acute exacerbation of COPD.[11,12] It is remarkable to observe that PTE was clinically suspected in less than half of the cases and that no specific symptoms were described, thus supporting the view that clinical suspicion of PTE in acute exacerbation of COPD is particularly difficult since clinical symptoms of decompensated COPD may closely mimic those of PTE. Thus, micro-thromboembolism may also contribute to clinical symptoms of an acute exacerbation of COPD. Pharmacological thromboprophylaxis should be instituted for the in-hospital management of these patients.

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The online version of this article contains a supplemental appendix.

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Second donation of hematopoietic stem cells from unrelated donors for patients with relapse or graft failure after allogeneic transplantation

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative approach for a variety of hematologic malignant and non-malignant disorders. With the rising number of stem cell transplantations from unrelated donors over the last years,[1] the occurrence of graft failure or disease relapse has increased. Therapeutic options for the majority of these patients include a second HCT using stem cells from the same unrelated donor.

Given the lower stem cell yield obtained by a bone marrow harvest, the easy and convenient access to G-CSF mobilized peripheral blood stem cells (PBSC) has resulted in their preferred usage as the source of hematopoietic progenitor cells.[2] Nevertheless, severe complications have been described.[3] In fact, we described[4] for the first time a significant increase in spleen size after G-CSF stimulation. Although there have been a few single case reports of the occurrence of secondary hematologic malignancies in voluntary stem cell donors after exposure to G-CSF,[5] at the moment long-term safety data for repeated G-CSF exposure for stem cell donors are not available. Additionally, a bone marrow harvest as an alternative donation procedure still harbors a minimal risk of morbidity.

Against this background, it is of importance to address the question whether repeated donations of HSC in case of graft failure or relapse are associated with a clinical benefit for patients thus justifying a possibly increased risk for voluntary donors. Earlier studies on this subject were mainly performed with bone marrow (BM) as stem cell source (SCS) and showed a worse outcome compared to results after first transplantation. Nevertheless, even the use of PBSC does not seem to have a positive