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COMMENTARY

Commentary on "The suboptimal fibrinolytic response in COVID-19 is dictated by high PAI-1"

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COVID-19 is associated with complex hemostatic changes, many of which are associated with disease severity and mortality risk.[1–3] Platelet hyperreactivity, a hypercoagulable state, and defective fibrinolysis have been consistently demonstrated by multiple laboratories. Some of these hemostatic changes persist following recovery from active COVID-19 infection and have been proposed to contribute to the post-COVID-19 syndrome.[4–6] Interestingly, despite a clear reduction in fibrinolytic capacity in *in vitro* tests, D-dimer levels and plasmin–antiplasmin complexes are highly elevated in patients with COVID-19, which indicates active ongoing fibrin breakdown which, however, may be inadequate to clear all fibrin generated. Laboratory evidence for a hypofibrinolytic state in COVID-19 patients has been demonstrated by prolonged plasma-based clot lysis times,[1] hypofibrinolytic profiles in viscoelastic testing,[2,7] and changes in fibrinolytic proteins,[1,2] including high levels of fibrinogen, plasminogen activator inhibitor 1 (PAI-1), and tissue plasminogen activator (tPA). However, the exact implications of these changes are incompletely understood. The study by Whyte et al.[8] in this issue of *Journal of Thrombosis and Haemostasis* aimed to investigate the main determinants of the fibrinolytic state in COVID-19, and showed that PAI-1 significantly contributes to the hypofibrinolytic state in these patients.

In a cohort of 113 hospitalized COVID-19 patients, levels of PAI-1 antigen and its stabilizing cofactor vitronectin were higher compared to 24 patients with non-COVID-19 respiratory infection and healthy controls. As the COVID-19 patients in this cohort had a significantly higher body mass index (BMI) compared to the non-COVID-19 respiratory infection patients, the difference in PAI-1 antigen levels might be at least partially attributable to increased secretion of PAI-1 by adipocytes (as for example in obesity[9]). However, as argued by the authors, the difference in BMI is unlikely to account for the difference in PAI-1 levels that is seen between these groups, as leptin levels were comparable between the groups and did not correlate with PAI-1 levels. Moreover, BMI did not correlate with PAI-1 levels either, and this is in line with a previous study in hospitalized COVID-19 patients, in which no association between BMI and PAI-1 levels was found.[2] Another explanation for the high PAI-1 levels in COVID-19 patients could be increased secretion of PAI-1 by activated platelets. It has been well established that platelet activation, for example by thrombin, results in release of PAI-1 from platelet alpha-granules,[10] although part of the released PAI-1 is retained on the platelet membrane.[11] Because both massive platelet activation and increased thrombin generation are central in COVID-19, platelets are a likely source of the elevated plasma PAI-1 in COVID-19 patients. A third explanation might be increased release of PAI-1 by endothelial cells, as endotheliopathy is a key feature of COVID-19 with autopsy studies showing severe endotheliopathy of the pulmonary vasculature.[12] Future studies into the source(s) of PAI-1 and mechanisms of PAI-1 release in COVID-19 would be of definite interest.

Plasma-based clot lysis times were increased in COVID-19 patients, and clot lysis times were strongly correlated to PAI-1 activity levels. Interestingly, whereas PAI-1 antigen and activity levels were elevated in COVID-19 and non-COVID-19 respiratory infection patients compared to controls, clots lysis times were only increased in the COVID-19 patients. The discrepancy may be explained by the selective increase in vitronectin levels in COVID-19 patients only.

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The source of the vitronectin elevation in COVID-19 patients is unclear, and it is also unclear why vitronectin does not increase in non-COVID-19 respiratory infection patients. Platelet-released vitronectin may account for the increase in plasma levels in COVID-19 patients, but the increase in plasma vitronectin may also be related to enhanced hepatic synthesis, as vitronectin is an acute phase protein (like for example fibrinogen).

In an effort to better understand by what the impaired fibrinolytic response in COVID-19 is driven, the authors performed clot lysis assays using tenecteplase, a tPA variant that is resistant to the inhibitory activity of PAI-1. Addition of tenecteplase to plasma of COVID-19 patients resulted in efficient clot lysis in all samples regardless of plasma PAI-1 concentration. In contrast, when clot lysis was initiated by alteplase, a substantially prolonged clot lysis time was observed in the majority of COVID-19 patient samples with medium to high levels of PAI-1 antigen. These results underline the critical contribution of PAI-1 to impaired fibrinolysis in COVID-19, and show the potential benefits of the use of the clinically available tenecteplase in COVID-19 patients. Thrombolytic therapy with the aim to reduce pulmonary symptoms in COVID-19 patients has been studied with encouraging initial results,[13] and larger follow-up studies are ongoing (NCT04640194). The majority of these studies have used alteplase, and as it is not unlikely that tenecteplase may have additional benefit. Future clinical studies using tenecteplase (for example NCT04505592) are of definite interest.

PAI-1 has previously been identified as the major determinant of hypofibrinolysis in other conditions, such as obesity, old age, and venous thrombosis.[9,14,15] In these studies, the increased thrombotic risk that is associated with these conditions was mainly attributed to high PAI-1 levels. Whether these findings can be extrapolated to COVID-19 and whether high PAI-1 levels increase the risk for macrovascular thrombosis has to be determined in a larger cohort study. It is tempting to speculate that PAI-1–associated hypofibrinolysis is a key contributor to both intrapulmonary thrombosis in active COVID-19 infection and to the ongoing prothrombotic state that has been proposed to contribute to long COVID. We have previously demonstrated marked elevations in PAI-1 levels and clot lysis time in COVID-19 patients up to 12 months after hospital discharge.[6] Although we attributed the sustained elevations in PAI-1 levels to obesity, the results of the present study suggest that an obesity-unrelated mechanism contributes. Assessing vitronectin levels longitudinally and in patients with documented post-COVID-19 syndrome would be of interest.

The relation between PAI-1 levels and progression of COVID-19 has not yet been established. Previous studies have reported higher PAI-1 levels in COVID-19 patients admitted to the intensive care unit compared to patients admitted to the ward.[1,2] However, in one of these studies,[1] when severity of disease was based on the level of respiratory support instead of level of care, there was no difference in PAI-1 levels between the three groups. On the contrary, in the study by Whyte et al.,[8] PAI-1 antigen levels, but not PAI-1 activity, were higher in patients receiving oxygen versus patients receiving no oxygen support. There was no effect of type of respiratory support on PAI-1 levels, but it should be noted that this cohort only included five patients on mechanical ventilation. The effect of mechanical ventilation on fibrinolysis in the lung has been studied in a rat model of lipopolysaccharide-induced lung injury, and mechanical ventilation resulted in higher PAI-1 activity, but not PAI-1 antigen levels, in the bronchoalveolar lavage fluid.[16] Although it remains uncertain whether this study can be extrapolated to humans, it suggests a possible effect of mechanical ventilation on PAI-1 levels and underlines the importance of adding a control group with non-COVID-19 patients on mechanical ventilation when studying mechanically ventilated COVID-19 patients. A relevant future study would focus on PAI-1 in the sickest COVID-19 patients with high mortality and thrombotic burden, as these patients have more profound alterations in their fibrinolytic state and presumably benefit most from thrombolytic strategies.

In conclusion, the study by Whyte et al.[8] showed that increased PAI-1 levels in patients with COVID-19 is the main determinant of the hypofibrinolytic state of these patients. Importantly, this study demonstrated improved efficiency of clot lysis by tenecteplase versus alteplase in plasma of COVID-19 patients with high levels of PAI-1. These results might guide future fibrinolytic strategies aimed at improving clinical outcome in COVID-19 patients. Future studies of the contribution of PAI-1 to thrombotic risk in COVID-19 and the potential of teneceteplase or PAI-1 inhibition in treating macro- and microvascular thrombotic complications in patients with COVID-19 would be of great value.

CONFLICT OF INTEREST

The author declares no competing interests.

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