For a long time, we have known that a decrease in fibrinolytic activity is linked to an increase in risk of myocardial infarction.1–3 Paradoxically, the most convincing association between fibrinolysis and cardiovascular risk was an increased level of the profibrinolytic enzyme itself, tissue plasminogen activator (tPA).4,5 This unexpected finding was said to be due to the methods of measurement, which were unable to distinguish free tPA from tPA complexed with various inhibitors, the most important one being plasminogen activator inhibitor 1 (PAI-1), but this explanation had never been proven.

See p 2019

Recently, specific 2-site ELISAs have been developed that allow independent measurements of complexes of tPA with its inhibitors PAI-1, C1′-inhibitor, and antiplasmin.6 In a substudy of the Stockholm Heart Epidemiology Program (SHEEP), Wiman and colleagues7 studied these particular components, as well as the more classic tPA and PAI-1 antigens, and PAI-1 activity in 1212 patients who were enrolled ~3 months after a myocardial infarction. The results of this case-control study are reported in the present issue of the Journal (p 2020).

The baseline measurements of the variables of interest were compared with the recurrence rate of myocardial infarction during a follow-up of 3 years. These parameters were also compared with other variables that are either known or suspected to correlate with a recurrence of cardiac events, such as lipids, fibrinogen, and von Willebrand factor (vWF). Eighty-six patients of the cohort (7.1%; 95% confidence interval, 5.7% to 8.7%) experienced reinfarction. When compared with matched patients from the cohort and also with matched healthy controls, these patients had significantly higher baseline plasma concentrations of fibrinogen, vWF, tPA antigen, PAI-1 activity, and tPA/PAI-1 complexes. These variables were also significantly higher in the patients as a group (with or without recurrence) compared with the healthy controls. In addition, Wiman et al7 observed a strong correlation between tPA/PAI-1 complexes and both PAI-1 activity and tPA antigen. Patients with values for tPA/PAI-1 complex or vWF >75th percentile of the controls had a reinfarction risk that was increased by 80% or 130%, respectively, which was statistically significant but might also appear to be clinically relevant, from both an individual and a societal point of view. These observations are in line with the results of the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study performed in 4 centers of the MONItoring trends and determinants in CARDiovascular disease (MONICA) program among >10 000 male participants.8 In that study, epidemiological evidence was provided for a role of fibrinogen and PAI-1 in the pathogenesis of coronary heart disease. As an additional hint, the present study suggests that the risks due to the increase in tPA/PAI-1 complexes and vWF might be additive. Despite these converging lines of evidence, the true clinical impact of these findings remains uncertain, because there is no proof that prescribing a more intensive secondary prophylaxis (which one?) to patients with these new risk markers would result in fewer reinfarctions in this subpopulation.

The biological mechanisms underlying the association of elevated tPA/PAI-1 or vWF with recurrent myocardial infarction are not yet clear. Do elevated concentrations of tPA/PAI-1 or vWF directly contribute to an increased risk of myocardial infarction, or are there common underlying mechanisms that may account for both an increased risk of reinfarction and the observed increased plasma concentrations of tPA/PAI-1 and vWF? Endothelial cell activation and inflammation might represent such mechanisms.

Increased vWF and tPA levels are often attributed to endothelial cell “damage” or “dysfunction.” However, it is highly unlikely that vWF and tPA are released from injured endothelium simply as a result of nonspecific cell damage. There is increasing evidence that both vWF and tPA are regulated secretory proteins that are stored and released from the same endothelial secretory granules, the Weibel-Palade bodies.9,10 Endothelial cells in culture in the short term release vWF11 and tPA9–12 in response to a multitude of agonists, such as thrombin, histamine, fibrin, complement, leukotrienes, purine nucleotides, and epinephrine, among others. Less-specific stimuli such as increased shear stress or tissue hypoxia have also been proposed. However, it is unclear at this stage how these observations relate to increased plasma levels in various pathophysiological conditions. In primates, experimental induction of disseminated intravascular blood coagulation quickly increased plasma levels of both tPA and vWF.13–15 To what extent chronic procoagulant conditions have an effect on tPA and vWF levels remains to be established. Treatment of endothelial cells with thrombin...
activates the thrombin receptor, which leads not only to the short-term release of tPA and vWF but also to an increased expression by endothelial cells of PAI-1 and tissue factor.2 Moreover, the presence of tissue factor in atherosclerotic plaque areas leads to coagulation, activation, and accumulation of fibrin deposits and to activation of nearby endothelial cells. Thus, under certain conditions, elevated tPA or vWF levels may be markers of endothelial cell activation, which is associated with an increased expression of tissue factor on the endothelial cell surface and an increased PAI-1 release.

An alternative underlying mechanism would be a vascular inflammatory state. Atherosclerotic lesions are infiltrated by macrophages and T lymphocytes that are able to release inflammatory mediators, with pronounced effects on endothelial cells producing vWF and tPA and on smooth muscle cells that produce tPA. In several studies, elevated levels of the acute-phase mediator interleukin-6 and of the acute-phase proteins fibrinogen and C-reactive protein were found to be associated with an increased risk of myocardial infarction.5,18,19 Recently, we observed in baboons that intravenous administration of interleukin-6 led to a marked increase of tPA and PAI-1 but not of vWF.14,15,20 In mice, tumor necrosis factor induces an increased expression of PAI-1 in endothelial cells and, interestingly, in adipocytes, providing a link between PAI-1, obesity, and inflammation.21 Chronic inflammatory conditions may thus have contributed to the increased concentrations of tPA and PAI-1 in the studied patient groups. Conversely, the association of elevated tPA/PAI-1 with reinfarction may reflect an association of the severity of the inflammatory condition with reinfarction. Measurements of interleukin-6 or C-reactive protein might settle to what extent chronic inflammation has contributed to the risk of reinfarction in the Swedish study.

Generally, tPA is considered to be a protective factor for the development of thrombotic disease. However, we cannot exclude the possibility that in the context of myocardial infarction, an elevated expression of tPA near the necrotic core would have pathogenic effects. Indeed, local proteolytic activity could contribute to destabilization of atherosclerotic plaques and thereby increase the risk of plaque rupture, which in turn leads to myocardial infarction.

The predictive value of vWF may be partly obscured by the fact that average vWF concentrations are 30% lower in group O blood donors than in group A or B blood donors.22 In contrast, the ABO blood group has no influence on plasma concentrations of vWF:antigen II, a 95-kDa protein released from pro-vWF and stored in equimolar amounts in Weibel-Palade bodies.23 It would therefore be interesting to investigate whether the predictive value of vWF:antigen II would be better than that of vWF.

In conclusion, the article of Wiman et al provides further confirmation of the association of hemostatic variables with cardiovascular risk. In population studies, the observed associations are consistent. It remains to be established, however, to what extent measurement of these factors may help to identify patients at elevated cardiovascular risk and whether this may have therapeutic consequences. A better understanding of the biological mechanisms underlying the association between cardiovascular risk and the various risk markers would be very useful and should be the subject of further study. Finally, a major difficulty in such studies is that measurements are always done in blood collected from peripheral veins, whereas cardiovascular events are also mediated by local phenomena.

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On the Association of Elevated tPA/PAI-1 Complex and von Willebrand Factor With Recurrent Myocardial Infarction
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