Defective fibrinolytic states as triggers of myocardial infarction: the cardiologist's view

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Disclosure of a specific prothrombotic/antifibrinolytic state by determination of plasminogen activator inhibitor type 1 (PAI-1), tissue-type plasminogen activator (t-PA), and t-PA/PAI-1 complex levels in plasma may help to define patients at high risk of developing acute coronary syndromes. According to the mechanisms of PAI-1 up-regulation, i.e. genetic factors, an activated renin-angiotensin-aldosterone system, and other atherosclerotic risk factors (hypertriglyceridemia, insulin resistance), PAI-1 plasma levels might be reduced by the action of antidiabetic drugs, fibrates, statins, as well as by inhibitors of the renin-angiotensin-aldosterone system, and this effect might contribute to the antiatherosclerotic and antithrombotic actions of these drugs. Moreover, PAI-1 resistant fibrinolytic agents may be beneficial in thrombolytic therapy of acute myocardial infarction.

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The fibrinolytic system and its role in acute coronary syndromes

Role of tissue-type plasminogen activator in acute coronary syndromes. Data from prospective studies indicate that the plasma concentration of tissue-type plasminogen activator (t-PA) is often elevated far in advance of a first acute myocardial infarction[1-6]. Recently, Thögersen et al.[7] were also able to demonstrate that the plasma levels of t-PA, of plasminogen activator inhibitor type 1 (PAI-1) and of von Willebrand factor are associated with the subsequent development of a first acute myocardial infarction, and showed further that for t-PA, but not for PAI-1 and von Willebrand factor, this association was independent of established risk factors. It is hypothesized that t-PA elevations reflect an adaptive and highly physiologic response to an increased risk for thromboembolic complications. In part, elevated t-PA antigen levels may reflect increased complex formation with elevated PAI-1 because most commercial t-PA antigen assays do not differentiate between free and "complexed" t-PA. Nevertheless, data suggest that the long-term effects of the fibrinolytic potential on cardiovascular risk may be mediated primarily by t-PA rather than by PAI-1[4,6].

Role of plasminogen activator inhibitor type 1 in acute coronary syndromes. Elevated PAI-1 plasma levels are associated with an increased incidence of acute coronary syndromes, including unstable angina, myocardial infarction, reinfarction, and sudden cardiac death[7-21].

Plasma PAI-1 levels peak in the early morning hours, when the incidence of acute myocardial infarction and of non-occlusive ischemic coronary events is highest[22-24].

Plasminogen activator inhibitor type 1 and failure of thrombolytic therapy in acute myocardial infarction. Several studies suggest that elevated pretreatment levels of PAI-1 may reduce the efficacy of thrombolytic therapy by preventing or retarding clot dissolution or by favoring early thrombotic reocclusion[10,25-33]. Increased formation of t-PA/PAI-1 complexes during thrombolysis[34,35] or a reactive increase of PAI-1 plasma levels after cessation of thrombolytic infusion[30,36-38] may contribute to a less successful effect of t-PA and of its mutants[33].

Tissue-type plasminogen activator/plasminogen activator inhibitor type 1 complexes in acute coronary disease. Recently, specific two-site ELISAs that allow independent measurements of t-PA/PAI-1 complexes have been developed. Wiman et al.[39] observed a strong correlation between t-PA/PAI-1 complexes and both t-PA antigen and PAI-1 activity. Patients with values of the t-PA/PAI-1 complex above the 75th percentile of control values had a reinfarc-

tion rate that was increased by 80%. The biological mechanisms underlying the association of elevated t-PA/PAI-1 complexes with recurrent myocardial infarction are not yet fully understood and may include: 1) a secondary reaction to endothelial cell activation triggered by prothrombotic mechanisms[40], and/or 2) vascular inflammation[41,42].

D-dimer and plasmin-antiplasmin complexes in acute coronary syndromes. D-dimer and plasmin-antiplasmin complexes are markers of hemostatic activation that assess the balance between procoagulant and fibrinolytic reactions. Both D-dimer[43-48] and plasmin-antiplasmin complexes[47] predicted future myocardial infarction and were independent of traditional risk factors for atherosclerosis, of PAI-1 and of C-reactive protein[47]. These findings confirm the hypothesis that activation of the endogenous fibrinolytic system usually occurs in advance of future coronary thrombotic events.

Regulation of circulating fibrinolytic parameters

Genetic regulation of plasminogen activator inhibitor type 1 and tissue-type plasminogen activator. The regulation of PAI-1 plasma levels partly depends on genetic mechanisms. At least three polymorphisms in the PAI-1 gene located on chromosome 7 have been shown to correlate with plasma levels of PAI-1: an eight-allele (CA)n repeat polymorphism in intron 3[49], a two-allele *Hind*III restriction fragment length polymorphism of the 3' flanking region[50], and a single guanosine insertion/deletion variation, the 4G/5G, whereby individuals with the 4G/4G polymorphism exhibit the highest PAI-1 plasma levels[51,52]. It was recently shown that individuals homozygous for the 4G allele also have higher levels of PAI-1 activity and antigen in platelets, thus indicating a possible higher resistance against endogenous and external plasminogen activation[53].

In contrast to PAI-1, genetic regulation of t-PA is not very well characterized and clinical applications of t-PA gene polymorphisms are lacking.

Association of plasminogen activator inhibitor type 1 and tissue-type plasminogen activator levels with risk factors for atherosclerosis. Metabolic disorders may be of greater importance for the up-regulation of PAI-1 plasma concentrations than genetic determinants[54]. Risk factors involved in the insulin-resistance syndrome and in diabetes, such as body mass index, waist-to-hip ratio, fasting insulin levels and triglyceride or HDL cholesterol levels, were related to increased PAI-1 plasma levels in both genders[52,54]. Samples taken at atherectomy from patients with diabetes contained substantially more PAI-1 than those taken from patients without diabetes[55]. Thus, diabetic patients are possibly more predisposed to local thrombus formation and its persistence after plaque rupture than non-diabetic individuals.

A positive correlation between insulin resistance and t-PA antigen levels has also been found[56]. In contrast to PAI-1, the t-PA plasma concentration is not dependent on triglycerides and on total cholesterol, whereas an association has been observed between increased levels of HDL cholesterol and low levels of t-PA[57].

Adipose tissue as a source of plasminogen activator inhibitor type 1. Obesity has been shown to be related with a reduced fibrinolytic response[58]. Adipose tissue itself may directly contribute to the elevated expression of PAI-1 in obesity[59,60]. Subcutaneous adipose tissue contains levels of PAI-1 mRNA which are 3-fold higher than those in visceral adipose tissue[61]. Because obesity is an important component of the insulin-resistance syndrome, combined stimulation of PAI-1 production by insulin-dependent mechanisms and by adipose tissue may have a strong influence on PAI-1 plasma levels and, therefore, contribute to the increased cardiovascular complications that characterize this disorder[62].

Influence of the renin-angiotensin-aldosterone system on endogenous fibrinolysis. Angiotensin-converting enzyme (ACE) down-regulates t-PA production via its degrading action on bradykinin, which is a stimulator of t-PA production *in vivo*[63]. In contrast, ACE up-regulates endothelial cell and smooth muscle cell PAI-1 production by the action of angiotensin II[64-68], via its degradation product angiotensin IV, which acts on a specific receptor (AT_4 receptor)[69] (Fig. 1).

Further determinants of plasminogen activator inhibitor type 1 and tissue-type plasminogen activator plasma levels. PAI-1 plasma levels may be further influenced by age, gender, circadian variations, estrogen, hypertension, fibrinogen, alcohol consumption, ciga-

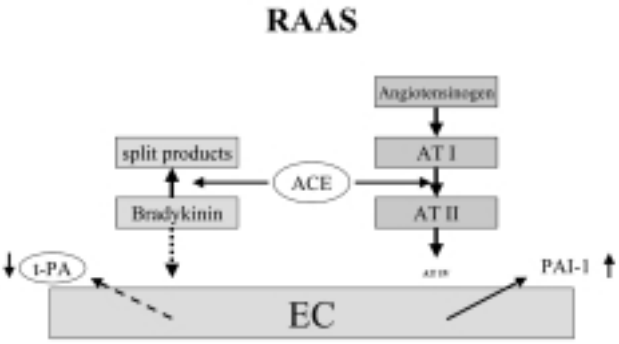

Figure 1. *The renin-angiotensin-aldosterone system (RAAS) and the regulation of fibrinolytic factors. Schematic illustration of the central role of the angiotensin-converting enzyme (ACE) at the interface between the renin-angiotensin system and the fibrinolytic system. Conversion of angiotensin I to angiotensin II by ACE leads to increased endothelial expression of plasminogen activator inhibitor type 1 (PAI-1), whereas degradation of bradykinin by ACE inhibits endothelial production of tissue-type plasminogen activator (t-PA). AT = angiotensin; EC = endothelial cell.*

rette smoking, diet, and physical activity[52,70-77]. t-PA plasma levels are also related to age, gender, circadian variations, alcohol consumption, and smoking[70,78-81].

Therapeutic means for improving the fibrinolytic capacity

Insulin treatment in type II diabetic patients reduced pro-insulin levels and PAI-1 activity independently of glycemic control[82]. Metformin caused a reduction in basal as well as in post-venous occlusion PAI-1 plasma levels and also decreased basal plasma levels of triglycerides and insulin[83-85]. The alpha-blocker doxazosin had beneficial effects on glucose and triglyceride metabolism, as well as on fibrinolysis[86,87]. Reductions in plasma triglyceride levels by gemfibrozil[88-90] and niacin[91] have been found to decrease PAI-1 plasma levels and PAI-1 mRNA expression. Treatment of hypercholesterolemia with statins may not only reduce plasma PAI-1 indirectly, by reducing cholesterol and triglyceride levels, but also through a direct "pleiomorphic" action of statins on human vascular smooth muscle and endothelial cells[92-94]. Weight loss significantly reduces plasma PAI-1 levels in obese humans[95-98]. The use of ACE-inhibitors increases the net fibrinolytic capacity, both by up-regulating t-PA and simultaneously by reducing PAI-1 plasma levels[99-106]. Intravenous enalapril can attenuate the thrombolysis-induced increase in PAI-1[37]; also blockade of the angiotensin II type 1 receptor is successful in decreasing PAI-1 plasma levels[104,105].

Investigators have searched for a PAI-1 resistant thrombolytic agent with increased potency, reduced bleeding risk, and capable of producing rapid, complete and sustained reperfusion. TNK-t-PA has been shown to combine these properties in the most favorable way. *In vitro* and animal studies have confirmed the theoretical advantages of TNK-t-PA[107-109]. However, in patients with acute myocardial infarction, these promising advantages could not be shown to improve the clinical outcome: the ASSENT II trial compared a weight-adjusted dose of TNK-t-PA with front-loaded t-PA and found equivalent mortality reduction (6.2%) and side effects for both agents[110]. Unfortunately, no specific determinations were performed to disclose possible special effects of TNK-t-PA vs t-PA in subgroups of patients with elevated pre-treatment PAI-1 levels. This is rather regretful as the concept of using a PAI-1 resistant fibrinolytic agent in patients with elevated PAI-1 levels at the beginning of thrombolytic therapy is of special interest.

Summary

PAI-1 plasma levels are regulated on a genetic basis, but their dependence on a series of other atherosclerotic risk factors among which hypertriglyceridemia and insulin resistance is more important. Recently, the role of an activated renin-angiotensin-aldosterone system in PAI-1 up-regulation and, subsequently, in the depression of endogenous fibrinolysis has been disclosed. It remains to be established, however, to what extent the determination of PAI-1, t-PA, and t-PA/PAI-1 complex plasma concentrations may help to identify patients at elevated cardiovascular risk. If so, this may have therapeutic consequences, as PAI-1 plasma levels can be reduced by the action of antidiabetic drugs, fibrates, statins, and by inhibitors of the renin-angiotensin-aldosterone system. The decrease in PAI-1 levels may contribute to the known antiatherosclerotic and antithrombotic actions of these substances and favorably influence the long-term outcome.

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