Int J Clin Lab Res 23:78–82, 1993

International Journal of Clinical & Laboratory RESEARCH

Predictive value for thrombotic disease of plasminogen activator inhibitor-1 plasma levels

Domenico Prisco, Elena Chiarantini, Maria Boddi, Carlo Rostagno, Andrea Colella, and Gian Franco Gensini

Clinica Medica I, Viale Morgagni 85, I-50134 Firenze, Italy

Summary. Plasminogen activator inhibitor-1 plays a major role in the fibrinolytic system as the main physiological inhibitor of both tissue-type and urinary-type plasminogen activators. The inhibitor is present in plasma in small amounts and derives mainly from endothelial cells. Positive correlations have been reported between plasma levels and different parameters, such as serum triglycerides, insulin plasma levels and body mass index. Moreover, high plasma inhibitor concentrations have been observed in different disease states, but it must be stressed that plasminogen activator inhibitor-1 behaves as an acute-phase reactant and measurement of plasma levels is not significant in the acute phase of the disease. A possible predictive value of inhibitor levels for thrombotic events such as deep vein thrombosis and ischemic heart disease has been studied. On the basis of available studies, the predictive value is not clear for venous thrombosis, whereas plasminogen activator inhibitor-1 levels can predict some coronary events, at least in subgroups of young patients with a first myocardial infarction. It remains to be established if treatments able to reduce plasma inhibitor levels lead to a decrease in the risk of thromboembolic events.

Key words: Fibrinolysis – Plasminogen activator inhibitor-1 – Deep vein thrombosis – Ischemic heart disease – Predictive value

Introduction

Plasminogen activators play a central role in the function of the fibrinolytic system. These activators, i.e., tissue-type (tPA) and urinary-type (uPA) are inhibited by at least four specific inhibitors [plasminogen activator inhibitors (PAI)] which have been the subject of intensive studies in the last decade. PAI-1 and PAI-2 have been widely investigated, while little information is available about PAI-3 and PAI-4 [44].

Offprint requests to: D. Prisco

Among the specific inhibitors, a pivotal role is played by PAI-1, the main physiological inhibitor of tPA and of uPA [22], which has been extensively studied in the last few years. In fact, some familial thrombophilic states associated with impaired fibrinolysis, previously attributed to a defective release of tPA, have been demonstrated to be due to high PAI activity [21].

Sites of PAI-1 formation

PAI-1 (endothelial cell-type PAI) is present in plasma in small amounts [8] and is stored in large amounts in alpha-granules of blood platelets [13], which account for more than 90% of PAI-1 present in the blood [4, 46]; however they are not the main source of plasma PAI-1. Plasma PAI-1 mostly derives from endothelium [5, 43]. The concentration of PAI-1 in platelet-rich plasma, after platelet lysis by sonication, is proportional to the platelet count [5]. In addition to endothelial cells [11], PAI-1 is synthesized by fibroblasts, smooth muscle cells [30], human hepatocytes [45] and by different neoplastic cell lines. In a recent study [42] carried out on extracts of human tissues obtained at necroscopy, in which the PAI-1 concentration was immunologically measured in many different tissues and organs, liver and spleen were found to be the organs in which PAI-1 was detectable at the highest concentration. In contrast, other tissues, such as myocardium or brain, contain hardly any PAI-1.

Physiological aspects

PAI-1 is a single-chain glycoprotein with a molecular weight of about 52 kDa composed of 379 amino acids. It is a serine protease inhibitor with a reactive-site peptide bond of Arg 346-Met 347. PAI-1 may be found in two different functional forms: active and latent. PAI-1 contained in endothelial cells is mostly in the active form, but when released it becomes inactive with a half-life of about 30 min [33]. The loss of plasminogen activator inhibitory

properties of active PAI-1 is probably due to a conformational change in the molecule. In contrast, in platelets 96%–97% of PAI-1 is in the inactive or latent form. In vitro activation of latent PAI-1 can be reversibly achieved with protein denaturants, such as sodium dodecyl sulfate and urea, and their removal with nonionic detergents induces renaturation [19].

Active PAI-1 forms complexes in a 1:1 stoichiometric ratio with tPA and inactivates it, in the same way as another inhibitor antithrombin III inactivates thrombin. PAI-1 reacts with single-chain and two-chain tPA and with two-chain uPA, but not with single-chain uPA or with the streptokinase-plasmin complex [29]. PAI-1 is stabilized in plasma by binding to protein S or vitronectin [9] but can be enzymatically inactivated by thrombin and activated protein C. The PAI-1 concentration can be measured by immunological assays (antigen, PAI-1 Ag) or by functional assays (activity, PAI activity). It should be stressed that assay of PAI activity is influenced by tPA levels.

A good correlation between plasma PAI-1 Ag and PAI-1 activity has been reported in normal subjects [50]; however in some clinical conditions the correlation may be poor [41]. Different assays are able to detect total PAI-1, free PAI-1 [40] and tPA-PAI-1 complexes [48].

In addition to inhibiting and modulating tPA and uPA activities, PAI-1 also exerts other physiological functions in the stabilization of the primary hemostatic plug. PAI-1 is released by aggregating platelets [38], and is able to bind to a fibrin clot [51] directly or via vitronectin, which is also secreted by aggregating platelets [38]. Fibrin-bound PAI-1 can still inhibit tPA and uPA activities and tPA-PAI-1 complexes compete with free tPA for fibrin binding, so decreasing the amount of free tPA adsorbed on fibrin [10]. Thus, spontaneous lysis of thrombi is strictly dependent on PAI-1 content, while in pharmacological thrombolysis the plasminogen content is a major factor [37]. In normal subjects plasma PAI activity fluctuates during the day, with the lowest values in the afternoon [28]. Total PAI-1 Ag plasma levels are higher in males than in females [49]. A similar pattern has been found for tPA-PAI-1 complex and free PAI-1 concentrations [27, 49]. A correlation between PAI levels and age was observed both in control subjects and in patients with ischemic heart disease (IHD) [1, 35]. This finding may account for the decrease in fibrinolytic activity reported with aging [34]. Finally, PAI-1 levels are higher in smokers than in nonsmokers [16].

PAI-1 in disease

A positive correlation has been reported in many studies between plasma PAI and triglyceride levels in patients with IHD and venous thrombosis [18, 24]. This is of particular interest, since, in the last few years, hypertriglyceridemia has been re-evaluated as a risk factor for thrombotic diseases [6, 7]. Moreover, positive correlations between PAI and insulin levels and between PAI and body mass index have also been reported [25, 36, 31]. The classical afternoon decrease of PAI-1 levels was reported to be more marked in obese than in normal people [27]. Plasma and platelet PAI-1 levels above normal values were reported in different diseases, such as myocardial infarction (MI) angina pectoris, arterial hypertension and type I and II diabetes [41]. Great variability in PAI-1 levels was observed in patients with acute inflammatory diseases or infection (hospitalized in emergency care units) [27]. In these patients, in whom classical biorhythms are suppressed, the absence of diurnal changes in PAI-1 suggests that different sources or regulatory mechanisms of PAI-1 production are involved [27]. In summary, high levels of PAI are not a specific index of disease, since plasma PAI-1 behaves as an acute-phase reactant [23], and so PAI-1 measurement is not meaningful in the acute phase of disease.

Conflicting results have been reported for deep venous thrombosis (DVT). Recently, in 123 young consecutive patients with a first episode of clinically diagnosed DVT, plasma PAI-1 Ag measured after the acute phase of disease (on average 14 weeks after phlebography and at least 2 weeks after the end of therapy) was not significantly different in patients with or without phlebographically confirmed DVT [32]. In particular, a similar percentage of patients in the two groups had PAI Ag levels higher than the control upper limit. In contrast, in other studies PAI-1 levels had been suggested to be a predictive index for DVT. Juhan-Vague et al. [24] investigated 120 patients with spontaneous or recurrent *idiopathic* DVT. Forty-four patients (36%) were poor-responders (euglobulin fibrinolytic activity increase less than twofold after venous stasis), and this was due to high PAI activity in 32 (72%). Finally, in a recent study performed on 77 patients with a history of *idiopathic* DVT and/or pulmonary embolism (1–144 months after the last acute episode), 22% of patients had elevated PAI-1 levels [15]. PAI-1 Ag determination before venous occlusion was found to be a sensitive (83%) and specific (89%) assay for the detection of patients with an impaired fibrinolytic response to venous occlusion; almost all patients (97%) with normal PAI-1 had a normal fibrinolytic response.

Conflicting results have also been obtained in *familial recurrent venous thrombosis*. Jorgensen and Bonnevie-Nielsen [21] reported elevated plasma levels of PAI activity in the members of a family with a tendency for recurrent DVT. However, in a large number of patients with venous thrombophilia, Engesser et al. [12] could not find a difference in PAI activity between patients with familial and patients with nonfamilial venous thrombotic disease.

Predictive value of PAI

Postoperative DVT

Many studies have been performed in patients undergoing selective surgery to assess the predictive value of preoperative fibrinolytic activity for postoperative DVT, but these studies can not be compared due to different preventive treatments, surgical techniques and diagnostic methods for DVT [39]. Overall, the available data suggest

an association between impaired preoperative fibrinolytic activity and postoperative thrombosis. PAI activity was determined in nine studies (6 in orthopedic surgery and 3 in general surgery) [39], and the results suggest that the impairment of fibrinolytic activity could be mainly caused by increased levels of PAI; however conclusive results are still lacking.

Ischemic heart disease

The first observations on a possible predictive value of high PAI levels for recurrences in patients with IHD were reported by Hamsten et al. [17] who studied 71 patients who had been affected by acute MI (AMI) before the age of 45 years, 3 years before the study. None of these patients suffered from any disease causing an increase in acute-phase proteins. The average basal PAI activity was much higher in patients than in controls. The value of high PAI levels as a "risk factor" persisted even if the analysis was corrected for other risk factors, such as body mass index, smoking and alcohol consumption, and in 38% of patients PAI activity was higher than the 90th percentile of control subjects. Moreover, tPA capacity (i.e., the difference in tPA activity levels under basal conditions and after venous occlusion) was lower in patients than in control subjects; in 37% of patients, tPA capacity was below the 10th percentile of the controls.

The same authors [18] studied 109 consecutive male patients, under the age of 45 years, who survived a first MI 3–6 months after the event; patients were followed for 3 years for evidence of reinfarction. Elevated PAI activity levels were found to represent an independent risk factor for reinfarction, not related to the severity of coronary artery lesions. The association between high PAI activity and the reinfarction rate was of little significance after an additional follow-up of 2–4 years [52].

Recently PAI activity levels were reported to be higher in unstable angina patients than in healthy controls [36]. Furthermore, high values of PAI activity, but not of PAI-1 Ag, were found in patients with unstable angina compared with either patients with stable-effort angina (despite a similar extent of coronary artery disease assessed by angiography) or controls [53].

In the last few years the role played by PAI in thrombolysis has been investigated. PAI-1 is a factor of crucial importance for the lysis of hemostatic clots (which contain variable amounts of PAI-1) mainly released by platelets. PAI-1 physiologically modulates lysis of blood clots, but this activity adversely affects the dissolution of thrombi in pathological states.

Recently, in subjects affected by AMI, PAI activity measured before thrombolytic therapy was found to be predictive of infarct artery reocclusion in the first 72 h (as assessed by coronary angiography performed 72 h after beginning of recombinant t-PA -r-tPA-infusion) [3]. In 42% of patients with occluded arteries, PAI activity was above the upper limit of controls. Two months later PAI activity plasma levels were similar in the two groups and not different from levels in healthy control subjects.

In another study patients with early recanalization (assessed 90 min after thrombolysis) had lower PAI activity on day 2 and day 3 after treatment than patients with persistent occlusion [2]. Early coronary recanalization could curtail the increase of PAI activity after AMI, most likely by reducing the extent of ischemia and necrosis and the consequent acute-phase reaction. The constantly elevated PAI-1 levels after coronary angioplasty may be closely related to an active evolving atheroma due to stimulation of PAI-1 release by immune and inflammatory mediators leading to restenosis [20]. Moreover, these elevated PAI-1 levels might also contribute to restenosis by impairing fibrinolytic capacity [20].

Conclusions

On the basis of all these data, the predictive power of PAI levels for venous thrombosis remains unclear but there is sufficient evidence that PAI levels can predict coronary thrombosis. This evidence has prompted investigation of the possibility of lowering PAI levels. Plasma PAI levels are positively correlated with triglycerides, insulin and body mass index, so suggesting that diet can influence PAI levels. Moreover, recent data indicate that physical exercise may also lead to a decrease in PAI levels. The effect of physical exercise has been studied in healthy old male subjects (60–82 years) following a program of intensive endurance exercise training, consisting in jogging, cycling and walking for about 45 min per session, 4 or 5 days per week for 6 months. After this period, PAI activity decreased by 58%, fibrinogen levels decreased by 13% and tPA activity increased by 39% [47]. A similar effect of physical exercise on PAI activity had previously been reported in patients undergoing a 6-month rehabilitation program of physical exercise after AMI [14]. However, the clinical relevance of a normalization of PAI-1 levels to reduce the incidence of thrombosis still needs to be fully investigated in prospective studies.

References

1. Aillaud MF, Pignol F, Alessi MC, Harle JR, Escande M, Mongin M, Juhan-Vague I, Increase in plasma concentration of plasminogen activator inhibitor, fibrinogen, von Willebrand factor, factor VIII:C and in erythrocyte sedimentation rate with age. Thromb Haemost 55:30, 1986
2. Andreotti F, Roncaglioni MC, Hackett DR, Khan MI, Regan S, Haider AW, Davies GJ, Kluft C, Maseri A, Early coronary reperfusion blunts the procoagulant response of plasminogen activator inhibitor-1 and von Willebrand factor in acute myocardial infarction. J Am Coll Cardiol 16:1553, 1990
3. Barbash GI, Hod H, Roth A, Miller HI, Rath S, Har Zahav Y, Modan M, Zivelin A, Laniado S, Seligsohn U, Correlation of baseline plasminogen activator inhibitor activity with patency of the infarct artery after thrombolytic therapy in acute myocardial infarction. Am J Cardiol 64:1231, 1989
4. Booth NA, Anderson JA, Bennett B, Platelet release protein which inhibits plasminogen activators. J Clin Pathol 38:825, 1985
5. Booth NA, Simpson AJ, Croli A, Bennett B, MacGregor IR, Plasminogen activator inhibitor (PAI-1) in plasma and platelets. Br J Haematol 70:327, 1988
6. Cambien F, Jacoveson A, Richard JL, Warnet JM, Ducimetiere P, Claude JR, Is the level of serum triglycerides a significant

predictor of coronary death in normocholesterolemic subjects? Am J Epidemiol 126:86, 1987
7. Carlsson LA, Aberg H, Serum triglycerides – an independent risk factor for myocardial infarction but not for angina pectoris. N Engl J Med 312:1127, 1985
8. Declerck PJ, Alessi MC, Verstreken MV, Kruithof EKO, Juhan-Vague I, Collen D, Measurement of plasminogen activator inhibitor 1 in biologic fluids with a murine monoclonal antibody-based enzyme-linked immunosorbent assay. Blood 71:220, 1988
9. Declerck PJ, De Mol M, Alessi MC, Baudner S, Paques EP, Preissner KT, Muller-Berghaus G, Collen D, Purification and characterization of a plasminogen activator inhibitor-1 binding protein from human plasma. Identification as a multimeric form of S protein (vitronectin). J Biol Chem 263:15454, 1988
10. Diéval J, Nguyen G, Gross S, Delobel J, Kruithof EKO, A lifelong bleeding disorder associated with a deficiency of plasminogen activator inhibitor type 1. Blood 77:528, 1991
11. Dosne AM, Dupuy E, Bodevin E, Partial characterization of a fibrinolytic inhibitor by cultured endothelial cells derived from human umbilical vein. Thromb Res 12:377, 1978
12. Engesser L, Brommer EJP, Kluft C, Briet E, Elevated plasminogen activator inhibitor (PAI), a cause of thrombophilia? A study in 203 patients with familial or sporadic venous thrombophilia. Thromb Haemost 62:672, 1989
13. Erickson LA, Ginsberg MH, Loskutoff DJ, Detection and partial characterization of an inhibitor of plasminogen activator in human platelets. J Clin Invest 74:1465, 1984
14. Estellés A, Aznar J, Tormo G, Sapena P, Tormo V, Espana F, Influence of a rehabilitation sports programme on the fibrinolytic activity of patients after myocardial infarction. Thromb Res 55:203, 1989
15. Grimaudo V, Bachmann F, Havert V, Christe MA, Kruithof EKO, Hypofibrinolysis in patients with a history of idiopathic deep vein thrombosis and/or pulmonary embolism. Thromb Haemost 67:397, 1992
16. Haire WD, Goldsmith JC, Rasmussen J, Abnormal fibrinolysis in healthy male cigarette smokers: role of plasminogen activators inhibitors. Am J Hematol 31:36, 1988
17. Hamsten A, Wiman B, Faire U de, Blomback M, Increased plasma levels of a rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. N Engl J Med 313:1557, 1985
18. Hamsten A, Faire U de, Walldius G, Dahlen G, Szamosi A, Landou C, Blomback M, Wiman B, Plasminogen activator inhibitor in plasma: risk factor for recurrent myocardial infarction. Lancet II:3, 1987
19. Hekman CM, Loskutoff DJ, Endothelial cells produce a latent inhibitor of plasminogen activators that can be activated by denaturants. J Biol Chem 260:11581, 1985
20. Huber K, Jorg M, Probst P, Schuster E, Lang I, Kaindl F, Binder BR, A decrease in plasminogen activator inhibitor-1 activity after successful percutaneous transluminal coronary angioplasty is associated with a significantly reduced risk for coronary restenosis. Thromb Haemost 67:209, 1992
21. Jorgensen M, Bonnevie-Nielsen V, Increased concentration of the fast-acting plasminogen activator inhibitor in plasma associated with familial venous thrombosis. Br J Haematol, 65:175, 1987
22. Juhan-Vague I, Moerman B, Cock F de, Aillaud MF, Collen D, Plasma levels of a specific inhibitor of tissue-type plasminogen activator (and urokinase) in normal and pathological conditions. Thromb Res 33:523, 1984
23. Juhan-Vague I, Aillaud MF, Cock F de, Philip-Joet C, Arnaud C, Seradimigni A, Collen D, The fast-acting inhibitor of tissue-type plasminogen activator in an acute phase reactant protein. In: Davidson JF, Donati MB, Coccheri S (eds) Progress in fibrinolysis. Churchill Livingstone, London, p 146, 1985
24. Juhan-Vague I, Alessi MC, Fossat C, Valadier J, Aillaud MF, Serradimigni A, Clinical relevance of reduced t-PA release and elevated PA inhibitor levels in patients with spontaneous or recurrent deep venous thrombosis. Thromb Haemost 57:67, 1987
25. Juhan-Vague I, Vague P, Alessi MC, Badier C, Valadier J, Ailaud MF, Atlan C, Relationships between plasma insulin, triglyceride, body mass index, and plasminogen activator inhibitor 1. Diabete Metab 13:331, 1987
26. Juhan-Vague I, Alessi MC, Joly P, Thirion X, Vague P, Declerck PJ, Serradimigni A, Collen D, Plasma plasminogen activator inhibitor-1 in angina pectoris. Influence of plasma insulin and acute-phase response. Arteriosclerosis 9:362, 1989
27. Juhan-Vague I, Alessi MC, Raccali D, Aillaud MF, Billerey M, Ansaldi J, Philip-Joet C, Vague P, Daytime fluctuation of plasminogen activator inhibitor 1 (PAI-1) in populations with high PAI-1 levels. Thromb Haemost 67:76, 1992
28. Kluft C, Jie AFH, Sprengers ED, Verheijen JH, Identification of a reversible inhibitor of plasminogen activators in blood plasma. FEBS Lett 190:315, 1985
29. Kruithof EKO, Gudinchet A, Bachmann F, Plasminogen activator inhibitor 1 and plasminogen activator inhibitor 2 in various disease states. Thromb Haemost 59:7, 1988
30. Laug WE, Vascular smooth muscle cells inhibit plasminogen activators secreted by endothelial cells. Thromb Haemost 20:165, 1985
31. Legnani C, Maccaferri M, Tonini P, Cassio A, Cacciari E, Coccheri S, Reduced fibrinolytic response in obese children: association with high baseline activity of the fast acting plasminogen activator inhibitor (PAI-1). Fibrinolysis 2:211, 1988
32. Levi M, Lensing AWA, Buller HR, Prandoni P, Dooijewaard G, Cuppini S, Cate JW ten, Deep vein thrombosis and fibrinolysis: defective urokinase type plasminogen activator release. Thromb Haemost 66:426, 1991
33. MacGregor IR, Booth NA, An enzyme-linked immunosorbent assay (ELISA) used to study the cellular secretion of endothelial plasminogen activator inhibitor (PAI-1). Thromb Haemost 59:68, 1988
34. Meade TW, Chakrabarti R, Haines AP, North WRS, Stirling Y, Characteristics affecting fibrinolytic activity and plasma fibrinogen concentrations. BMJ 1:153, 1979
35. Mehta J, Mehta P, Lawson D, Saldeen T, Plasma tissue plasminogen activator inhibitor levels in coronary artery disease: correlation with age and serum triglyceride concentration. J Am Coll Cardiol 9:263, 1987
36. Munkvad S, Jespersen J, Gram J, Kluft C, Interrelationship between coagulant activity and tissue-type plasminogen activator (t-PA) system in acute ischaemic heart disease. Possible role of the endothelium. J Int Med Res 228:361, 1990
37. Potter Van Loon BJ, Rijken DC, Brommer EJP, Van Der Maas APC, The amount of plasminogen, tissue-type plasminogen activator and plasminogen activator inhibitor type 1 in human thrombi and the reaction to ex-vivo lysibility. Thromb Haemost 67:101, 1992
38. Preissner KT, Holzhuter S, Justus C, Muller-Berghaus G, Identification and partial characterization of platelet vitronectin: evidence for complex formation with platelet-derived plasminogen activator inhibitor-1. Blood 74:1989, 1990
39. Prins MH, Hirsh J, A critical review of the evidence supporting a relationship between impaired fibrinolytic activity and venous thromboembolism. Arch Intern Med 151:1721, 1991
40. Ranby M, Sundell IB, Nilsson TK, Blood collection in strong acidic citrate anticoagulant used in a study of dietary influence on basal tPA activity. Thromb Haemost 62:917, 1989
41. Simpson AJ, Booth NA, Moore NR, Bennett B, The platelet and plasma pools of plasminogen activator inhibitor (PAI-1) vary independently in disease. Br J Haematol 75:543, 1990
42. Simpson AJ, Booth NA, Moore NR, Bennett B, Distribution of plasminogen activator inhibitor (PAI-1) in tissues. J Clin Pathol 44:139, 1991
43. Sprengers ED, A sensitive assay, specific for endothelial cell type plasminogen activator inhibitor in blood plasma. Thromb Haemost 55:74, 1986

44. Sprengers ED, Kluft C, Plasminogen activator inhibitors. Blood 69:381, 1987
45. Sprengers ED, Princen HMG, Kooistra T, Van Hinsbergh VWM, Inhibition of plasminogen activators by conditioned medium of human hepatocytes and hepatoma cell line Hep G2. J Lab Clin Med 105:751, 1985
46. Sprengers ED, Akkerman JWN, Jansen BG, Blood platelet plasminogen activator inhibitor: two different pools of endothelial cell type plasminogen activator inhibitor in human blood. Thromb Haemost 55:325, 1986
47. Stratton JR, Chandler WL, Schwartz RS, Cerqueira MD, Levy WC, Kahn Se, Larson VG, Cain KC, Beard JC, Abrass IB, Effects of physical conditioning on fibrinolytic variables and fibrinogen in young and old healthy adults. Circulation 83:1692, 1991
48. Takada Y, Takada A, Measurement of the concentration of free plasminogen activator inhibitor (PAI-1) and its complex with tissue plasminogen activator activator in human plasma. Thromb Res Suppl 8:15, 1988
49. Urano T, Sumiyoshi K, Nakamura M, Mori T, Takada Y, Takada A, Fluctuation of tPA and PAI-1 antigen levels in plasma: difference of their fluctuation patterns between male and female. Thromb Res 60:133, 1990
50. Urdén G, Hamsten A, Wiman B, Comparison of plasminogen activator inhibitor activity and antigen in plasma samples. Clin Chim Acta 169:189, 1987
51. Wagner OF, Vries C de, Hohmann C, Veerman H, Pannekoek H, Interaction between plasminogen activator inhibitor type 1 (PAI-1) bound to fibrin and either tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen acitvator (u-PA). J Clin Invest 84:647, 1989
52. Wiman B, Hamsten A, Abnormal fibrinolysis as an etiologic factor in thromboembolic disease (abstract). Thromb Haemost 62:13, 1989
53. Zalewski A, Shi Y, Nardone D, Bravette B, Weinstock P, Fischman D, Wilson P, Goldberg S, Levin DC, Bjornsson TD, Evidence for reduced fibrinolytic activity in unstable angina at rest: clinical, biochemical, and angiographic correlates. Circulation 83:1685, 1991