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D-Dimer increase after percutaneous transluminal angioplasty and clinical recurrence after primary revascularization in acute myocardial infarction? A pilot study

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Abstract It has been reported that the increase of plasminogen activator inhibitor-1 activity immediately after elective coronary angioplasty is related to subsequent clinical recurrence in patients with chronic coronary artery disease. The aims of our study were to evaluate the behavior of plasminogen activator inhibitor-1 and D-Dimer after revascularization in acute myocardial infarction patients treated with angioplasty and stenting and if this behavior is predictive of subsequent clinical recurrence. D-Dimer and plasminogen activator inhibitor-1 activity were evaluated in two groups of patients. Group 1 consisted of 54 consecutive patients undergoing primary angioplasty for acute myocardial infarction and Group 2 consisted of 48 patients undergoing elective angioplasty. Patients underwent control coronary angiography only in the case of clinical recurrence and/or positivity of provocative tests. D-Dimer and plasminogen activator inhibitor-1 baseline levels were significantly higher in group 1 than in group 2 ($P<0.0005$ and $P<0.05$, respectively). The percentage of group 1 patients with a post-procedural increase in D-Dimer was significantly higher among those with subsequent clinical recurrence with restenosis (61%) than among those with no recurrence (25%, $P<0.05$). No difference was observed in group 2. The percentage of group 2 patients in whom no decrease of plasminogen activator inhibitor-1 was observed after angioplasty was significantly higher (83%) among those with subsequent recurrence than among those with no recurrence (38%, $P<0.05$). This pattern was not observed in group 1. In conclusion, the role of early changes in plasminogen activator inhibitor-1 in predicting clinical recurrence after primary angioplasty in acute myocardial infarction patients is less clear than that observed after elective angioplasty. A significant role seems to be played by a more-marked clotting activation with increased fibrin formation.

Key words Percutaneous transluminal angioplasty • Primary revascularization • D-Dimer • Plasminogen activator inhibitor-1 • Clinical recurrence • Stent

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Introduction

There is evidence that high plasma plasminogen activator inhibitor-1 (PAI-1) concentrations are associated with the progression of coronary artery disease (CAD) and the development of myocardial infarction (MI) [1]. High plasma PAI-1 levels predict subsequent MI in patients with stable angina pectoris [2], and are associated with angiographic evidence of progressive CAD in young men with a history of MI [3]. In previous studies we have demonstrated that a post-procedural PAI-1 activity increase within 1 h of elective coronary revascularization is related to subsequent clinical recurrence due to restenosis in patients with chronic CAD treated with balloon percutaneous transluminal coronary angioplasty (PTCA) either without [4] or with [5] stent implantation. Over the last few years, intracoronary stents have become an essential component of the catheter-based treatment of CAD. The evidence indicates that stenting improves clinical outcome in a wide variety of clinical settings and lesion types [6]. We found that stent implantation, in comparison with balloon dilation without stent, was associated with an increased fibrin formation, as assessed by D-dimer increase,

immediately after PTCA, but the increase was not related to the risk of subsequent clinical recurrence [5]. Because fewer data are available for patients with acute MI (AMI) undergoing primary PTCA, the present prospective pilot study was planned to investigate: (1) the behavior of PAI-1 activity and D-dimer after revascularization in patients with AMI treated with PTCA and stent implantation; (2) if this behavior is predictive of subsequent clinical recurrence. As controls we studied a group of patients with chronic CAD, similar for age, sex, and clinical characteristics (except for the recent AMI) treated with the same procedure.

Materials and methods

Patients

Two groups of consecutive CAD patients, referred to the Haemodynamic Unit, Department of Medical and Surgical Critical Care (University of Florence) for PTCA and stent implantation, were enrolled in this study after having obtained their informed consent. Group 1 included consecutive patients who underwent primary PTCA for AMI and group 2 patients with CAD who underwent an elective balloon PTCA and were selected for stent implantation. All patients gave their informed consent to the use of part of their blood for research purposes, and all procedures were in accordance with the Helsinki Declaration.

Selection for group 1 was made on the basis of physical examination and a resting 12-lead electrocardiogram (ECG). MI was defined using the WHO criteria [7]: with typical chest pain lasting for longer than 30 min, ST elevation of 1 mm in two or more successive leads, or left bundle branch block. Exclusion criteria for group 2 were enzymatic or ECG evidence of AMI, clinical evidence of recent MI (less than 6 months), and unstable angina class III (according to Braunwald) [8]. Patients with immunological disorders or neoplastic disease were excluded from the study. Patients were also excluded if they had undergone surgical or invasive procedures in the month preceding the study. Thus, 107 patients (57 in group 1 and 50 in group 2) were included in the study. In group 2, 14 patients had stable effort angina, 12 unstable angina, class II B according to Braunwald, and 24 had no symptoms but had a stress test positive for ischemia. All group 2 patients were on standard antianginal therapy, and 36 were already on antithrombotic treatment [acetylsalicylic acid (ASA)] before the procedure.

Coronary angioplasty

Primary PTCA, to treat the occluded infarct-related artery (IRA), was performed using standard techniques. PTCA was performed through the femoral approach with a steerable balloon catheter using the Judkins' technique [9]. After initial coronary angiography, performed with low-osmolar non-ionic contrast, 10,000 IU heparin and 0.5 g ASA were infused i.v. in all patients immediately before the insertion of the dilatation catheter system and a continuous infusion of heparin (1,000 IU/h) was administered during the whole procedure and continued overnight. All patients received an i.v. infusion of nitroglycerin (5 γ/min) and an intracoronary bolus of nitroglycerin (250·γ) or isosorbide dinitrate (200·γ) before dilatation. Coronary stenting was performed using standard techniques, including high-pressure dilatations after stent deployment. No patient received glycoprotein IIb/IIIa receptor antagonists, because all procedures were performed before their widespread use in the management of acute coronary syndromes.

The coronary flow was graded according to TIMI flow rate [10], and coronary occlusion was defined as TIMI 0 in the IRA. PTCA success was defined as ≤40% residual stenosis associated with TIMI grade 3 flow, without major complications. Experienced angiographers, who were not involved in the performance of the procedures and were blinded to the laboratory results and to the clinical outcome, reviewed all angiograms. Angiograms were analyzed with a quantitative visual assessment according to a modification of the Brown-Dodge method, as previously reported [11, 12].

Blood sampling

Blood was collected before and immediately after (within 60 min) PTCA from the antecubital vein using a 19-G butterfly with minimal venous occlusion. The first 5 ml of venous blood was discarded. Blood was drawn directly into plastic tubes containing sodium citrate 0.129 M (1/10, v/v) for the determination of cross-linked fibrin degradation products (D-dimer) and PAI-1; aliquots of citrated blood, placed on melting ice after sampling, were then centrifuged within 10 min at 1,500 *g* for 20 min at 4° C, and plasma was stored at -80° C.

Laboratory methods

D-Dimer (control value <60 ng/ml) plasma levels were evaluated by ELISA (D-dimer test Gold, Agen Biomedicals, Brisbane, Australia). PAI-1 activity (control range 3–15 IU/ml) was determined according to Chmielewska et al. [13], using a commercial kit [Spectrolyse (fibrin), Bio-Pool, Umea, Sweden]. In preliminary experiments the presence of heparin up to 4 IU/ml did not affect the results of different tests.

Follow-up

Patients were followed clinically for a mean of 18 months. All patients were followed by clinical examination at 1 month, 6 months, and 1 year after PTCA. Ergometric test (Bruce protocol) [14] was performed in patients with one-vessel disease, and stress test with ^{201}Tl-scintigraphy in those with two- or three-vessel disease, at 1 month, 6 months, and 1 year. Reinfarction was defined as recurrent chest pain with new ST segment elevation associated with cardiac enzyme elevation. Recurrent ischemia was defined as effort or rest angina with documented ST segment or T wave changes. During the follow-up period, for ethical reasons, angiography was again performed only in patients with clinical recurrence or positive treadmill test, or a positive stress test with ^{201}Tl-scintigraphy. Angiographic restenosis was defined by the presence of a decrease >50% of gain in luminal diameter achieved post PTCA.

Statistical analysis

The results are expressed as median and range because of their skewed distribution. Preliminary statistical analysis was performed using the Wilcoxon's signed rank test or Fisher's exact test. Correlations between variables were calculated with Pearson product-moment correlation coefficients. Logistic regression analysis was used to determine multivariate predictors of clinical restenosis, after adjustment for indication to PTCA and clinical-angiographic variables, as well as the amount of contrast medium injected. *P* values of <0.05 were considered significant.

Results

Clinical outcome

In 57 group 1 patients (49 men and 8 women) primary PTCA was successfully performed and stents were delivered to the lesion. No patient needed emergency aorto-coronary bypass surgery. Nevertheless, 1 female patient underwent abrupt closure after PTCA and 2 patients (1 men and 1 women) underwent reocclusion of the vessel during the 1st week; these patients were excluded from the study. Therefore, 54 patients were enrolled in group 1 and during follow-up 18 (33%) patients had recurrence of ischemia and underwent angiography. Restenosis was demonstrated in all.

In 50 group 2 patients (44 men and 6 women) two procedures (in 2 male patients with effort angina who were excluded from the study) were unsuccessful and 48 were successful; in all patients stents were delivered to the lesion. In this group no patient underwent abrupt closure or reocclusion of the vessel during the 1st week. During the follow-up, 6 (12.5%) patients had recurrence of ischemia and underwent angiography. In all patients restenosis was demonstrated.

No significant correlation was found between clinical recurrence and indication for PTCA, risk factors for cardiovascular disease, or clinical variables (data not shown). Clinical characteristics of the 102 patients included in the study are shown in Table 1.

Changes of hemostatic parameters after PTCA

D-Dimer baseline values were significantly higher in group 1 than in group 2 ($P<0.0005$). In both groups, post-PTCA D-dimer levels were significantly higher than baseline (group 1 $P<0.005$ and group 2 $P<0.0005$, Table 2). Baseline values of PAI-1 activity were significantly higher in group 1 than in group 2 patients ($P<0.05$). PAI-1 activity did not show any significant change at the end of the procedure in group 1, whereas a slight but significant decrease was observed in group 2 ($P<0.05$) (Table 2). At the end of the procedure, PAI-1 levels were significantly higher in group 1 than in group 2 patients ($P<0.05$).

Clinical restenosis

No significant difference was found between patients with and without restenosis-related clinical recurrence with regard to D-dimer baseline levels, but the levels in group 1 patients with no clinical restenosis were significantly higher than in group 2 ($P<0.01$). In group 1, D-dimer levels at the end of the procedure were higher in patients with sub-

Table 1 Characteristic of study population (*CAD* coronary artery disease, *BMI* body mass index, *AMI* acute myocardial infraction, *HDL* high-density lipoprotein)

	Group 1	Group 2
No. of patients	54	48
Male/female	48/6	42/6
Age	60 (44–75)	65 (38–81)
Family CAD history	28	26
BMI	26 (19–34)	27 (16–36)
Smoking habits	28	20
Hypertension	26	26
Mean systolic blood pressure (mmHg)	150 (100–190)	140 (120–170)
Mean diastolic blood pressure (mmHg)	85 (70–100)	80 (65–95)
Diabetes mellitus	4	10
Previous AMI	4	12
Total cholesterol (mg/dl)	210 (150–320)	223 (180–241)
HDL-cholesterol (mg/dl)	38 (25–69)	36 (26–81)
Triglycerides (mg/dl)	153 (79–900)	170 (88–420)

sequent clinical recurrence than in those without ($P<0.005$), whereas such a difference was not found in group 2 patients (Table 3). In group 1 an increase in D-dimer after PTCA occurred in 11 of 18 patients with subsequent recurrence (61%), but only in 9 of 36 patients without (25%, $P<0.05$).

After PTCA a non-significant trend towards an increase in median PAI-1 levels was observed in patients with clinical restenosis in both groups, whereas PAI-1 significantly decreased in group 2 patients without subsequent recurrence ($P<0.005$, Table 3). Thus, post-PTCA PAI-1 levels were significantly higher in group 2 patients with recurrence compared with those without ($P<0.05$), whereas no significant differences were found in group 1. In group 2 a decrease in PAI-1 after PTCA occurred in 26 of 42 (62%) patients without subsequent recurrence, and in only 1 of 6 patients with recurrence (17%, $P<0.05$).

Table 2 D-Dimer and plasminogen activator inhibitor-1 (PAI-1) activity levels in the two groups (*PTCA* percutaneous transluminal coronary angioplasty)

	Group 1 (n=54)	Group 2 (n=48)
D-Dimer (ng/ml)		
before PTCA	55 (10–810)	29.0 (2–135)*5
after PTCA	62 (6–1,097)*2	69 (10–284)*3
PAI-1 (IU/ml)		
before PTCA	9 (1.4–37.0)	6.0 (2.4–14.8)*4
after PTCA	9 (3–38)	4.0 (3.1–15.0)*1, *4

*1$P<0.05$ vs. baseline levels, *2$P<0.005$ vs. baseline levels, *3$P<0.0005$ vs. baseline levels, *4$P<0.05$ vs. group 1 levels, *5$P<0.0005$ vs. group 1 levels

Discussion

Restenosis after successful PTCA remains the major limitation of this procedure [15, 16]. Thrombin is implicated in mechanisms related to restenosis [17, 18]. However, measurement of thrombin generation and thrombin activity during PTCA have yielded conflicting results. In previous studies we have observed that, unlike coagulation, the study of fibrinolysis (especially of PAI-1 activity) immediately after elective PTCA may provide prognostic information about the risk of clinical recurrence [4, 5]. In the present study we have made preliminary observations in patients with AMI undergoing primary PTCA with stenting. The results of this study indicate that an increase in D-dimer immediately after primary PTCA tends to be associated with an increased risk of clinical recurrence due to restenosis in patients with AMI. A similar trend was not found for PAI-1 changes after PTCA. In chronic CAD patients, PAI-1 changes were more strictly related to subsequent recurrence than D-dimer changes after PTCA, as previously observed [4, 5].

In baseline samples taken before PTCA, AMI patients (group 1) were characterized by higher D-dimer and PAI-1 levels than chronic CAD patients (group 2), in agreement with previous studies [19, 20]. In AMI patients, as a whole, PTCA was followed by a slight increase in D-dimer, whereas PAI-1 activity did not change. However, if we look at those AMI patients with subsequent recurrence, the increase in D-dimer was more marked and a trend, although not significant, to a post-procedural increase in PAI-1 was found. In group 2, PTCA was followed by an increase in D-dimer and a decrease in PAI-1. However, those patients in whom PAI-1 levels were not decreased after the procedure were at higher risk of clinical recurrence.

Table 3 D-Dimer and PAI-1 in relation to restenosis-related clinical recurrence

	Group 1		Group 2	
	No clinical restenosis (n=36)	Clinical restenosis (n=18)	No clinical restenosis (n=42)	Clinical restenosis (n=6)
D-Dimer (ng/ml)				
before PTCA	56 (10–148)	47 (19–810)	28 (6–135)*6	38 (2–53)
after PTCA	57 (6–136)	81 (25–1097)*2, *3	69 (10–284)*1	54 (25–85)*5
No. of patients with D-dimer increase after PTCA	9/36	11/18*7	17/42	2/6
PAI-1 (IU/ml)				
before PTCA	9 (1.4–37)	9.1 (7.6–17.1)	5.5 (2.4–14.8)*5	8.1 (4.2–12.7)
after PTCA	8.1 (3–38)	12.9 (3–14.3)	3.8 (3.1–10.2)*1	12.0 (3.9–15.0)*4
No. of patients with PAI-1 decrease after PTCA	23/36	9/18	26/42	1/6*7

*1$P<0.005$ vs. baseline levels, *2$P<0.001$ vs. baseline levels, *3$P<0.005$ vs. no clinical restenosis, *4$P<0.005$ vs. no clinical restenosis, *5$P<0.05$ vs. group 1, *6$P<0.01$ vs. group 1, *7χ^2 $P<0.05$

Considering these observations with those of our previous study [5], stent application seems to be the main determinant of D-dimer increase after PTCA in most chronic CAD patients, whereas in AMI patients, in whom coronary thrombosis causes an enhanced fibrin formation and degradation before the procedure, only a minor further increase may be found in most patients after revascularization. However, among AMI patients a clear-cut increase occurred more frequently in those patients with subsequent recurrence, which suggests that a more-marked clotting activation with fibrin formation may play a role in the pathophysiology of late PTCA complications in these patients.

Although a trend was observed between post-PTCA PAI-1 increase and subsequent restenosis-related clinical recurrence in AMI patients, this relationship was not as clear-cut as that we observed in patients who underwent elective PTCA either with [5] or without [4] stent implantation. This discrepancy is probably related to biological differences between patients with AMI and those with chronic CAD. We can speculate that after PTCA fibrinolytic shutdown and clotting activation may play different roles in the clinical outcome of the two groups of patients.

Restenosis after PTCA may result from the response to injury of the vessel wall [21] and thrombin may play a central role in this mechanism via its different actions [21, 22]. Depending on the activity of the clotting and fibrinolytic system, a mural thrombus may persist, so maintaining a vicious cycle. In the present study, to assess clotting activation and fibrin deposition we measured plasma D-dimer, because its levels reflect the physiological response to fibrin formation and have been recently demonstrated in epidemiological studies to be a more-promising risk marker for thrombosis than other activation markers [23]. Moreover, D-dimer has a relatively long plasma half-life and its measurement has fewer problems related to blood sampling and pre-analytical errors. D-Dimer, which reflects fibrin turnover, has uniformly and strongly been positively associated with an increased CAD incidence [24]. This association is somewhat surprising, because higher levels of D-dimer in young, healthy subjects have been reported to reflect enhanced, not impaired fibrinolysis [25]. In reality, in CAD patients increased D-dimer reflects increased fibrin production, with resulting increased fibrin turnover, rather than identifying subjects with increased fibrinolysis.

If we accept that increased D-dimer levels may indirectly reflect an increased clotting activation with thrombin formation, our results suggest that, even if during PTCA high-dose heparin inhibits thrombin generation in most patients [21, 26], a further significant activation of coagulation may still occur in some patients with AMI. In AMI patients, fibrin formation is higher than in chronic CAD patients [19], and is further increased after PTCA, especially in patients with subsequent restenosis-related clinical recurrence. Interestingly, Salvioni et al. [27] demonstrated that the acute fibrinopeptide A (a marker of thrombin activity) response to PTCA has a predictive value for late restenosis. The clinical implications of this observation should be evaluated in ad hoc designed studies.

This study is a preliminary investigation performed on a limited number of patients with a low number of index events (especially in group 2), so that its conclusions should await confirmation by other groups. It is important to emphasize that, due to ethical reasons, only patients with clinical recurrence or with positive provocative tests during follow-up underwent control coronary angiography. Thus, this study does not permit any conclusion on the role of PAI-1 and D-dimer in angiographic restenosis, but only in clinical recurrence associated with restenosis. It is likely that some asymptomatic patients had angiographic restenosis, especially in group 2, in which only 6 of 48 patients had clinical restenosis versus 18 of 54 in group 1.

In conclusion, the role of early PAI-1 changes in predicting clinical recurrence after primary PTCA in AMI patients is less clear than after elective PTCA. In these patients a significant role may be played by a more-marked clotting activation, as reflected by an increase in D-dimer levels. Further studies on larger numbers of patients should assess the role of D-dimer in predicting late clinical recurrence after primary PTCA and the efficacy of more-intensive anticoagulant treatment in selected patients.

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