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Importance of Continued Activation of Thrombin Reflected by Fibrinopeptide A to the Efficacy of Thrombolysis

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Factors responsible for initial success or failure of coronary thrombolysis and persistent recanalization or early reocclusion have not been thoroughly elucidated. Both adequate initial clot lysis and preclusion of rethrombosis are required. Failure may reflect clot lysis followed immediately or somewhat later by rethrombosis. To determine whether differences in the intensity and persistence of the activation of thrombin are determinants of success or failure of recanalization, plasma fibrinopeptide A, a fibrinogen product liberated by thrombin, was serially assayed in 19 patients treated with intravenous streptokinase. In patients exhibiting recanalization (n = 9), plasma fibrinopeptide A decreased after administration of streptokinase but before administration of heparin. In patients without initially apparent recanalization, fibrinopeptide A increased, suggesting ongoing thrombosis, and subsequently decreased promptly after heparin. In patients with initial recanalization followed by overt reocclusion the pattern was different. Despite recanalization, fibrinopeptide A continued to rise markedly. Elevations persisted despite administration of heparin. Thus, inhibition of activation of thrombin is associated with successful recanalization. Conversely, persistent activation of thrombin may be a predisposing factor to both apparent initial failure of recanalization and overt early reocclusion.

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Factors responsible for the initial success or failure of thrombolysis and for early reocclusion have not been elucidated fully. Activation of plasminogen by itself may be sufficient for persistent recanalization without anticoagulation in some patients. In others, apparent failure of initial lysis or lack of persistence of recanalization may occur despite adequate activation of plasminogen (1) and may reflect intense or persistent activation of thrombin.

Fibrinopeptide A is a small polypeptide liberated from fibrinogen by the action of thrombin (2). Elevation of plasma fibrinopeptide A is a marker of ongoing thrombosis (2–5). Early after the onset of acute transmural infarction, fibrinopeptide A is frequently elevated. Values then decrease over 24 hours (6). Elevations of fibrinopeptide A indicative of ongoing intravascular coagulation decrease promptly in response to administration of heparin because of inhibition of thrombin coupled with the short half-life (3 to 5 minutes) of circulating fibrinopeptide A (6,7). Patients with angiographically documented coronary thrombosis consistently manifest marked elevations of plasma fibrinopeptide A. Thus, in the setting of acute transmural infarction, fibrinopeptide A appears to be a marker of coronary thrombosis (6).

To identify relations among ongoing thrombosis, initial success or failure of coronary thrombolysis and early reocclusion after initial recanalization, we assayed plasma fibrinopeptide A serially in 19 patients treated with intravenous streptokinase. We hypothesized that initial failure of thrombolysis and early reocclusion might reflect intense or persistent activation of thrombin in vivo. Cross-reactivity of fibrinogen degradation products in the fibrinopeptide A immunoassay was excluded. Results indicated that successful recanalization is associated with a prompt diminution of activation of thrombin. In contrast, persistent activation of thrombin is associated with and is a potential determinant of initial failure of coronary thrombolysis and of early reocclusion.

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Methods

Study patients. The clinical protocol employed in this study was approved by the Washington University Human Studies Committee. Patients were eligible for treatment with intravenous streptokinase if they were evaluated within 8 hours of the onset of symptoms of myocardial ischemia and if they exhibited more than 1 mm of ST segment elevation in two contiguous echocardiographic leads and were less than 76 years of age. Exclusion criteria included impaired hemostasis, recent major surgery, malignancy, long-term treatment with anticoagulants or severely limited venous access. After written informed consent had been obtained, streptokinase was given in doses of 750,000 to 1,000,000 U administered intravenously over 1 hour. Administration of heparin was initiated when the activated partial thromboplastin time had declined to 2.5 times normal. A bolus injection of at least 50 U/kg was followed by a continuous infusion of 1,000 U/h subsequently titrated to maintain the partial thromboplastin time at 2.5 times control.

Criteria of coronary recanalization determined prospectively included sudden resolution of ST segment elevation with development of Q waves on the electrocardiogram, relief of chest pain, sudden ventricular ectopic activity considered to be indicative of reperfusion arrhythmia and peaking of plasma creatine kinase activity within 10 hours or less of the onset of therapy. Serial electrocardiograms were obtained before administration of streptokinase, immediately after the onset of infusion, whenever clinical signs of reperfusion occurred and 24 hours after treatment with streptokinase. The presence or absence of reperfusion was determined by two investigators who did not know the fibrinopeptide A values.

Whenever possible, coronary angiography was performed within 48 hours. Patients who were subjected to cardiac catheterization later and in whom angiography was essential for classification are noted in the text. Coronary thrombosis was considered to be present when complete occlusion of the infarct-related vessel could be documented definitively.

Acquisition and assay of fibrinopeptide A in blood samples. Samples obtained at the time of admission were assayed for fibrinopeptide A, creatine kinase MB isoenzyme activity (CK-MB), prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, fibrin(ogen) degradation products and euglobulin lysis time. Because of the risk of spurious elevation of fibrinopeptide A in samples drawn inappropriately, samples were obtained only by technicians trained specially and evaluated periodically by the responsible investigators who evaluated them with an explicit quality control protocol (6,8). Fibrinopeptide A samples were drawn through a heparin lock flushed with heparinized saline solution (100 U/ml) before administration of streptokinase, before administration of heparin and either 15 or 60 minutes after administration of heparin. Samples were obtained for assay of CK-MB activity every 2 hours for at least 24 hours.

Prothrombin time, activated partial thromboplastin time, thrombin time, antithrombin 3 and euglobulin lysis time were assayed conventionally. Fibrinogen was assayed by the Ellis method and fibrinogen degradation products with the latex bead procedure (9,10). Blood samples for assay of fibrinopeptide A were drawn into tubes containing 1.58×10^{-1} *M* ethylenediaminetetraacetic acid and 1.47×10^{6} KIU/liter aprotinin, cooled rapidly to 0 to 4°C, centrifuged immediately at 1,000 *g*, frozen at −20°C for 24 hours and maintained at −70°C before radioimmunoassay with antibody provided by Mallinckrodt, Inc. The upper limit of normal for fibrinopeptide A in our laboratory is 2.0 ng/ml (6). Samples for CK-MB were drawn in tubes containing 8 m*M* ethyleneglycoltetraacetic acid and 12 m*M* mercaptoethanol, centrifuged immediately, refrigerated and assayed within 10 hours as described previously (11).

Separation of fibrinopeptide A by gel chromatography for exclusion of fibrinogen degradation products. A 1 × 18 cm Sephadex G-50 column was equilibrated with 120 m*M* sodium chloride, 2.7 m*M* potassium chloride, and 10 m*M* phosphate buffer pH 7.4, saturated with bovine serum albumin and washed with the same buffer until the effluent had an optical density of less than 0.01. Fibrinopeptide A standard (200 μl, 40 ng/ml) or a bentonite-treated patient plasma sample was applied to the column and eluted with equilibrating buffer. Each 0 to 73 fraction containing fibrinopeptide A was identified by radioimmunoassay of fibrinopeptide A.

Statistical analysis. Data are reported as mean ± SE. Fibrinopeptide A, CK-MB and partial thromboplastin values and time from onset of symptoms to treatment were normalized by log transformation before statistical analysis with *t* tests and a repeated measures analysis of variance with the use of the SAS statistical program (SAS Institute) and the computer facilities of the Washington University Biomedical Computer Laboratory.

Results

Clinical observations. Deep Q waves indicative of transmural myocardial infarction developed in 17 of the 19 patients. Infarction was excluded in one patient; in the other patient, non-Q wave infarction was present. Twelve patients with transmural infarction manifested criteria for initial recanalization after administration of streptokinase (Table 1). Recurrent chest pain, echocardiographic changes and elevations of CK-MB were not observed in 9 of these 12 patients (Group I). The other three patients with criteria of initial recanalization manifested recurrent chest pain, ST segment elevation and elevation of CK-MB indicative of

Table 1. Criteria of Reperfusion

Patient No.	Group	Time to Peak CK (hours)		ECG Criteria Present	Documentation by Coronary Angiography
		After Onset of Symptoms	After Onset of SK		
Patients With Initial Reperfusion					
1	I	13 5	9.0	Yes	Yes
2	I	14 5	6 5	Yes	No
3	I	19.0	10.0	Yes	Yes
4	I	8.0	5.5	Yes	No
5	I	16.0	10 0	Yes	No
6	I	8.5	7 5	Yes	Yes
7	I	11.0	9.0	Yes	Yes
8	I	8.25	6.0	Yes	Yes
9	I	8.5	6.0	Yes	Yes
10	II	11.5	7 0	Yes	Yes
11	II	9.75	6 75	Yes	Yes
12	II	9 0	7 25	Yes	No
Total (n = 12)		11.5 ± 1 0	7.54 ± 0.5	12/12	8/12
Patients Without Reperfusion					
13	III	25.5	19 0	None	Yes
14	III	24.5	21	None	No
15	III	21.0	12.5	None	No
16	III	18	11.5	None	Yes
17	III	19.0	16.0	None	Yes
Total (n = 5)		21.6 ± 1.5*	17 6 ± 2 5*	0/5	3/5

Data expressed as mean ± SE. *$p < 0.001$ between patients with and without reperfusion CK = creatine kinase; ECG = electrocardiographic; SK = streptokinase

reinfarction (Group II). Five other patients did not exhibit criteria of initial recanalization (Group III). The characteristics of each of these three groups are shown in Table 2. Age, gender and locus of infarction were similar among them. In patients with apparent initial failure of recanalization, administration of streptokinase had been initiated somewhat, but not significantly, later after the onset of symptoms (5.4 ± 1.1 hours compared with 4.0 ± 0.9 [Group I] and 3.2 ± 0.7 hours [Group II] [$p = 0.14$]). No bleeding complications requiring transfusion were encountered. The two patients without transmural infarction were considered separately.

Coronary angiography. This procedure was performed in 11 patients. In all, angiography confirmed the clinical impression. Each of the three patients with successful recanalization who did not undergo angiography exhibited prompt, early peaking of plasma creatine kinase activity (6.5, 5.5 and 10 hours after treatment, respectively) and electrocardiographic changes indicative of reperfusion. The two patients who did not manifest criteria of thrombolysis and who did not undergo angiography exhibited plasma CK values that peaked 21 and 12.5 hours after treatment, that is, 21 and 24.5 hours, respectively, after the onset of symptoms. Two of the three patients with reinfarction underwent

Table 2. Group Comparisons

Variable	Group I, Lysis (n = 9)	Group II, Reocclusion (n = 3)	Group III, Nonlysis (n = 5)
Gender	6M/3F	1M/2F	4M/1F
Age (yr) (±SD)	59.7 ± 2.9	53 0 ± 4.9	57.6 ± 3 1
Locus of myocardial infarction	6 ANT/3 INF	2 ANT/1 INF	2 ANT/3 INF
Time from onset to administration of streptokinase (hours)	4.0 ± 0 9	3 2 ± 0 7	5 4 ± 1 1
Initial fibrinopeptide A (ng/ml)	84.9 ± 38 1	49.2 ± 11.7	87.8 ± 69 2

ANT = anterior infarct; F = female, INF = inferior infarct, M = male.

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Table 3. Changes in Coagulation Variables

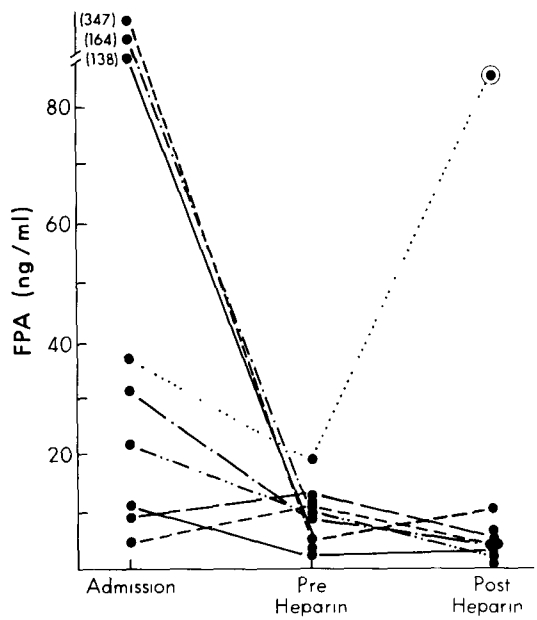
Variable	Group I, Reperfusion (n = 9)	Group II, Reocclusion (n = 3)	Group III, No Reperfusion (n = 5)
Activated partial thromboplastin time (seconds) (norm = 26 to 37)			
Baseline	30.4 ± 3 3	25.5 ± 0.8	29.8 ± 2.8
After streptokinase	72.4 ± 12.9	48 2 ± 1.2	96 2 ± 22.5
After heparin	71 7 ± 17 2	97 2 ± 26.7	104.6 ± 18.7
Fibrinogen (mg/ml) (norm = 150 to 360)			
Baseline	344 1 ± 60 6	341.7 ± 73.7	355.6 ± 29.9
After streptokinase	152.9 ± 31.8	136 7 ± 23.5	153.8 ± 21.6
Fibrinogen degradation product (μg/ml) (norm < 8.0)			
Baseline	17 0 ± 8.9	2.0 ± 1.0	6.0 ± 2.8
After streptokinase	268.9 ± 168.9	1,845.3 ± 1,639.5	153.6 ± 91.5

Data expressed as mean ± SE. norm = normal value.

coronary angiography, one immediately after reinfarction and one later after the onset of symptoms suggestive of recurrent infarction. The one patient with a non-Q wave infarction had a 60% occlusion of the infarct-related vessel.

Evaluation of the lytic state. In all patients in each of the three groups, a systemic lytic state reflecting the elaboration of plasmin in the circulating blood was evident (Table 3). Criteria of intact hemostasis were comparable in all three groups before administration of streptokinase. Before administration of heparin, the partial thromboplastin time was prolonged in all patients. In four patients with initial recanalization (Group I), one without (Group III) and all three patients with initial recanalization followed by reocclusion (Group II) the partial thromboplastin time had decreased to below two times control after streptokinase but before administration of heparin. After the first dose of heparin, partial thromboplastin time was greater than 2.5 times control in every patient. It fell to less than 2 times control while heparin was being infused only in four patients with initial recanalization. None exhibited criteria of reinfarction. The apparent difference in values for fibrinogen degradation products in Groups I and III and Group II were not statistically significant and were attributable primarily to the values of one patient in Group II with a marked elevation of degradation products (>5,120 μg/ml).

Figure 1. Group I. Serial fibrinopeptide A (FPA) values in patients with reperfusion (n = 9). The **circled value** indicates the value in a sample that had been obtained only with difficulty and it may be spuriously elevated.



Values for fibrinopeptide A. Initial fibrinopeptide A values were elevated markedly (>8 ng/ml) in patients with transmural infarction and were comparable among Group I patients with initially successful recanalization (n = 9) compared with Group III patients without recanalization (n = 5) (84.9 ± 38.1 and 87.8 ± 69.2 ng/ml, respectively). Initial fibrinopeptide A averaged 49.2 ± 11.7 ng/ml in patients with initial recanalization followed by reocclusion (Group II).

By the time heparin was initiated, 3.5 ± 1 hours after initial treatment with streptokinase, marked differences in plasma fibrinopeptide A values were evident among the three groups. In patients with persistent recanalization (Group I), fibrinopeptide A had declined by 88% when partial thromboplastin time had declined to 2.5 times control. Fibrinopeptide A values in this group changed very little after administration of heparin (Fig. 1). In the five patients without initial recanalization (Group III), fibrinopeptide A increased with time despite prolongation of the partial thromboplastin time after administration of streptokinase. Before administration of heparin, fibrinopeptide A values exceeded initial values by 57%, having risen markedly in four of the five patients. Within 1 hour after administration of heparin, fibrinopeptide A fell markedly to less than 50% of values in samples before administration of heparin (Fig. 2).

Among the three patients with recanalization in whom reinfarction occurred (Group II), elevation of fibrinopeptide

A was of a magnitude similar to that in patients without initially successful recanalization. However, the partial thromboplastin time was less prolonged than that in patients without initial recanalization. After administration of heparin, partial thromboplastin time exceeded two times control in all patients in this group. However, fibrinopeptide A remained markedly elevated (83.3 ± 21.4 ng/ml) (Fig. 3). Elevations evident 15 minutes after administration of heparin persisted in samples drawn 1 hour later.

These patterns of response of fibrinopeptide A to streptokinase and to heparin were significantly different in the three groups of patients with transmural infarction ($p < 0.05$, by analysis of variance for repeated measures) (Fig. 4). In the two patients in whom transmural infarction was excluded despite the induction of a fibrinolytic state comparable with that in Groups I, II and III (data not shown), minimally elevated levels of fibrinopeptide A initially changed only slightly after administration of streptokinase and heparin (Fig. 5).

In samples with marked elevations of fibrinopeptide A, assays were repeated after gel filtration chromatography of the samples, on Sephadex 50 by radioimmunoassay of the column eluate. Fibrinopeptide A immunoreactivity was evident only in fractions containing low molecular weight species excluding immunoreactivity of the fibrinopeptide A antibody with large fibrinogen degradation fragments such as X, Y or E.

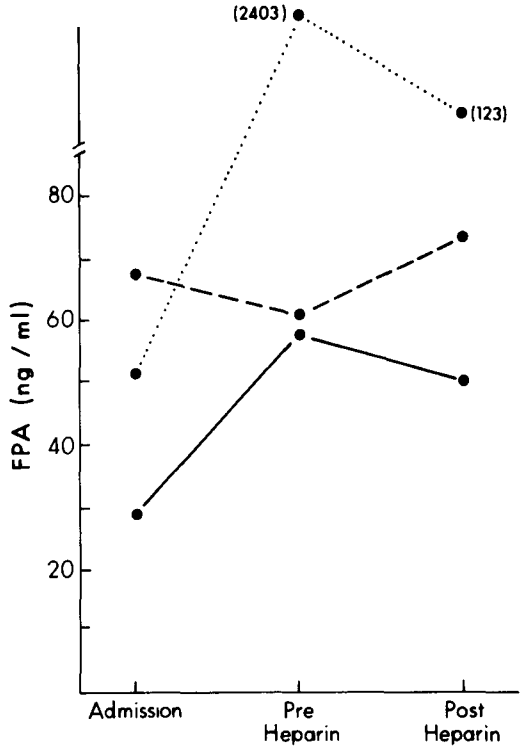
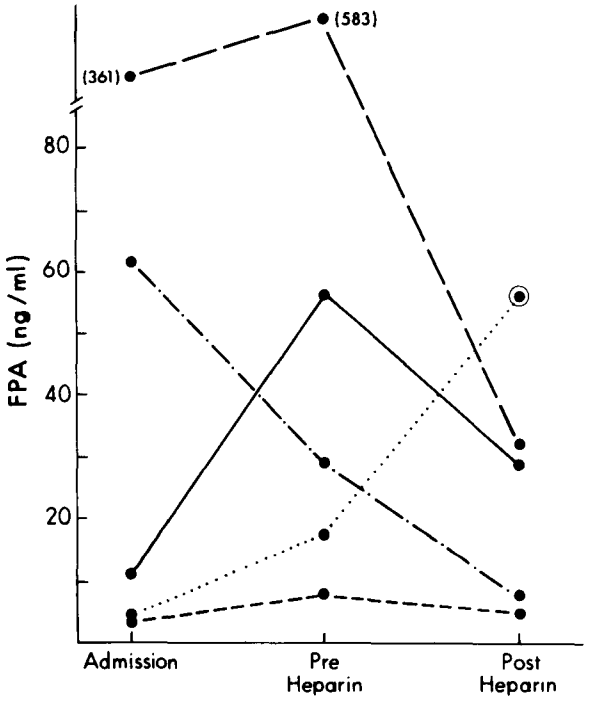


Figure 3. Group II. Serial fibrinopeptide A values in patients with reperfusion and reocclusion (n = 3). Values rise concomitantly with administration of streptokinase and do not decline sharply after administration of heparin, in contrast to Figure 2.

Figure 2. Group III. Serial fibrinopeptide A (FPA) values in patients without reperfusion (n = 5). In contrast to Figure 1, values rise concomitantly with administration of streptokinase but decline after heparin. The **circled value** indicates the value in a sample obtained only with difficulty and it may be spuriously elevated.



Antithrombin 3 was measured in samples from patients in whom fibrinopeptide A did not plummet in response to heparin. Values were normal in each case, indicating that induction of anticoagulant activity by heparin was not compromised and could not account for the persistent elevations of fibrinopeptide A.

Discussion

The results obtained in this study indicate that coronary thrombolysis with streptokinase is associated generally with a decline in activation of thrombin in vivo reflected by diminution of fibrinopeptide A activity in plasma, and that both initial failure of recanalization and reocclusion early after initial success may reflect excessive, persistent activation of thrombin in vivo.

We have shown previously (6) that fibrinopeptide A in plasma is markedly elevated early after the onset of symptoms of transmural myocardial infarction and that values generally decline over the subsequent 24 hours. In samples obtained more than 10 hours after the onset of transmural infarction or in those from patients with non-Q wave infarction, marked elevations of fibrinopeptide A are absent. In view of the prompt reduction in fibrinopeptide A after administration of heparin and the lack of a relation between the magnitude of elevation of fibrinopeptide A and the extent

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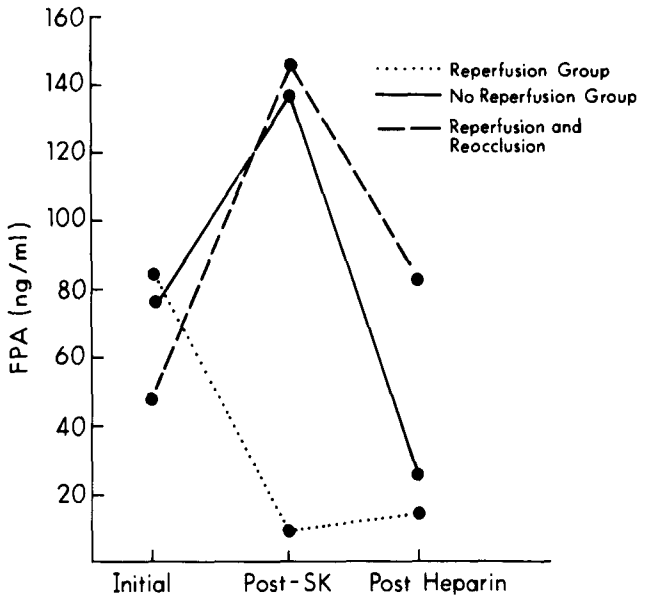
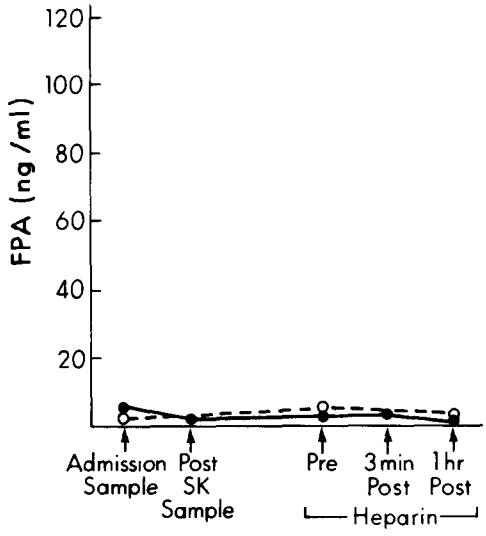


Figure 4. Pattern of change of fibrinopeptide A for the three groups. Mean fibrinopeptide A (FPA) ± SE is shown for each group. SK = streptokinase.

of infarction assessed by serial assays of CK-MB, fibrinopeptide A appears to be a marker of coronary thrombosis in this setting.

Lack of cross-reactivity of fibrin(ogen) degradation products in the fibrinopeptide A assay system. Radioimmunoassay results for fibrinopeptide A in samples from patients treated with streptokinase may be confounded by immunologic cross-reactivity of the antibody used with relatively large fibrinogen degradation fragments containing the NH_2 terminus of fibrinogen (12). Greater specificity can be achieved with some antibodies (2) such as those used in our study. The following factors argue strongly against cross-reactivity of fibrinogen degradation products in the assay system used in this study: the observed reduction of fibrinopeptide A after administration of streptokinase in patients exhibiting recanalization; the lack of elevation of fibrinopeptide A after administration of streptokinase despite marked elevations of fibrinogen degradation products in samples from patients without transmural infarction; the prompt decrease of fibrinopeptide A after administration of heparin in most patients while the concentration of fibrinogen degradation products in plasma continued to increase; and the distribution of fibrinopeptide A immunoreactivity in fractions separated by gel filtration columns.

Figure 5. Serial fibrinopeptide A (FPA) values in two patients without transmural infarction. Fibrinopeptide A did not increase despite fibrinogenolysis. SK = streptokinase.



Cross-reactivity of our fibrinopeptide A assay with the alpha 1-23 fibrinogen product of proteolysis induced by plasmin cannot be excluded unequivocally (13,14). In our study, elevations of fibrinopeptide A did not occur in patients without transmural infarction, despite administration of streptokinase which would have elicited production of this product with cross-reactivity if it were detectable. Thus, our assay, similar to the assays of Nossel et al. (15) and Kockum (14), appears to be free from significant influence by the alpha 1-23 product.

Thrombosis and thrombolysis: a precarious balance. Our results indicate that a relative balance between ongoing activation of thrombin and thrombolysis is a major determinant of the success or failure of persistent recanalization after coronary thrombolysis. Activation of plasminogen in the systemic circulation does not necessarily assure a successful clinical outcome (1). Reocclusion after initial recanalization occurs in as many as 43% of patients (16), especially when high grade residual stenosis is present (17). Accordingly, heparin or antiplatelet drugs, or both, are generally used concomitantly with activators of the fibrinolytic system. However, judging from our results, successful recanalization appears to be associated with a reduction in activation of thrombin before administration of heparin. Thus, activation of plasminogen may elicit a reduction in endogenous stimuli to thrombosis. The propensity toward activation of thrombin initially present may be modulated by local factors such as activation of protein C by thrombomodulin (18) or by accumulating fibrinogen degradation products with antithrombin effects, such as X, Y and E (19,20).

Mechanisms contributing to an imbalance between ongoing activation of thrombin (thrombosis) and lytic activity (thrombolysis) in patients in whom recanalization is not persistent have not yet been elucidated. Patients without persistent recanalization manifest more intense and more persistent activation of thrombin than that seen in patients with successful recanalization. The increased predilection to thrombosis may reflect reduced inhibition by thrombomodulin activation of protein C (18), persistence of greater amounts of functional thrombin within the thrombus or high

grade residual stenosis (17,21), among other factors. Relative or absolute differences in concentrations of higher molecular weight fibrinogen degradation products, such as X, Y or E, that inhibit activation of thrombin may contribute (19,20).

Patients with initial recanalization followed by reocclusion exhibit serial changes of plasma fibrinopeptide A similar to those in patients without initially successful recanalization. The pattern appears to be indicative of ongoing activation of thrombin in both. Pharmacologically induced lysis may predominate initially, despite marked underlying ongoing activation of thrombin in juxtaposition to high grade residual stenosis (17). With time, however, the ongoing activation of thrombin may predominate, with consequent reocclusion. The high propensity to thrombosis implicated by persistent elevations of fibrinopeptide A despite heparinization implies that more aggressive or earlier administration of heparin might prevent reocclusion in appropriate patients. Some patients with acute myocardial infarction require large amounts of heparin to inhibit production of fibrinopeptide A (7). This could be due to deficiency of antithrombin 3 (heparin cofactor); however, antithrombin 3 values were normal in our patients with elevations of fibrinopeptide A resistant to heparinization.

Mechanical interventions designed to improve coronary patency may be required to prevent reocclusion. Nevertheless, patients prone to early reocclusion may be identifiable prospectively because of persistent elevations of fibrinopeptide A despite adequate heparinization.

Imbalance between thrombosis and thrombolysis is a determinant of venous thrombosis in patients recovering from surgery (22), and temporally dyssynchronous thrombosis and lysis have been documented by analysis of the extent of γ-γ cross-linking in fibrin in clots (23).

Clinical implications. Although coronary angiography was not performed immediately because placement of catheters in the central circulation elevates fibrinopeptide A (24), the clinical criteria used prospectively separated groups without overlap. Statistically significant differences in the temporal pattern of elevations of fibrinopeptide A in plasma were observed among groups despite the small numbers of patients studied. Only in Group II (initial recanalization followed by early reocclusion) would a misclassification potentially distort results. The marked resistance of fibrinopeptide A elevations to administration of heparin was seen only in this group.

The marked reduction in activation of thrombin reflected by the rapid decline of plasma fibrinopeptide A in patients in whom coronary thrombolysis is successful implies that less aggressive anticoagulation than that used routinely may suffice for appropriately selected patients, with consequent reduction in the risk of bleeding. Alternatively, increases in plasma fibrinopeptide A in patients in whom recanalization is not achieved and in those with initial recanalization followed by early reocclusion appear to be indicative of a continuing stimulus to thrombosis. Aggressive and early anticoagulation or early mechanical revascularization, or both, may be needed in patients manifesting this phenomenon.

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