Fibrinolytic defect in chronic back pain

A controlled study of plasminogen activator activity in 20 patients

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We analyzed the fibrinolytic system in patients with chronic low back pain using a venous occlusion test to stimulate fibrinolysis, and we subsequently determined the levels of tissue plasminogen activator (TPA) and fast-acting inhibitor of TPA (PAI). There were 20 patients with a mean age of 50 years. Two thirds had radiographically spinal stenosis. Scar tissue around the spinal nerves was seen in 11 cases. Thirteen patients had undergone back surgery, whereas 21 healthy subjects served as controls. In the basal samples, TPA activity was decreased in the patients while TPA antigen level was increased compared with the controls. No clear explanation for this defective function of TPA in the patients was obtained, because no difference was seen in PAI level in basal samples. After the venous occlusion, no difference was observed in TPA activity between the two groups excluding the constitutionally defective fibrinolytic system in the patients. However, our results confirm low basal fibrinolytic activity in patients with chronic low back pain with manifest spinal pathology.

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Fibrin formation is a typical feature of degenerative disease in the spine. Therefore, defective fibrinolysis has been suggested to be an etiologic factor in chronic low back pain. Indeed, low fibrinolytic activity in blood has been described in patients with chronic low back pain (Jayson et al. 1984), in symptomatic spondylosis, and in arachnoiditis (Pountain et al. 1987). Based on studies of patients with acute low back pain and sciatica, Klimiuk et al. (1987) suggested that the fibrinolytic defect was secondary to mechanical damage. If persistent, however, it might become a secondary pathogenic factor contributing to chronicity of low back pain.

Intravascular fibrinolysis is based on rapid release of tissue plasminogen activator (TPA) from the endothelium in response to various stimuli (Hedner and Nilsson 1981). The activity of TPA is regulated by a specific fast-acting inhibitor of TPA (PAI; Hessel and Kluft 1986). In previous studies of fibrinolytic activity in chronic low back pain, fibrinolysis has been measured mainly by the euglobulin clot lysis time assay (Jayson et al. 1984, Klimiuk et al. 1987, Pountain et al. 1987). This a semiquantitative method, and it does not differentiate between the effects TPA and PAI on fibrinolysis.

We studied the fibrinolytic system in patients with chronic low back pain using a venous occlusion test to stimulate fibrinolysis and determined the levels of TPA and PAI.

Patients and methods

The series comprised 10 male and 10 female patients with a mean age of 50 (± 10) years. All the patients had a history of low back pain for more than 1 year. The mean Oswestry disability index (Fairbank et al. 1980) was 49 (± 13) percent and the Visual Analogue Scale (max 100 mm) 46 (± 16) mm, indicating severe disability and pain. Thirteen patients (8 were smokers) had used pain-relieving medication for 10 days before the study. Thirteen patients had undergone back surgery, but not during the last year.

All the patients underwent myelography, and if needed, computed tomography. Thirteen patients had radiographically central or lateral spinal stenosis. The narrowest sagittal distance in the lumbar area was measured by myelography, and the central stenosis was considered severe if less than 10 mm and moderate if between 10 and 13 mm. Lateral stenosis was considered severe if the nerve sheets were totally obliterated and moderate if only deformed. Scar tissue around the nerves was evaluated from CT

Table 1. Radiographic findings in the 20 patients

	Central stenosis	Lateral stenosis	Scar tissue	Arachnoiditis
No evidence	9	11	9	15
Moderate	5	6	9	2
Severe	6	3	2	3

examinations and arachnoiditis from myelograms. Scar tissue around the nerves was seen in 11 cases and arachnoiditis in 4 cases (Table 1). Evaluation of the severity was based on a grading scale developed for this study. The radiographic grading was made by 2 of the authors. In all the patients, there was at least one pathologic radiographic finding. None had evidence of ankylosing spondylitis in the sacroiliac joints. The erythrocyte sedimentation rate, hemoglobin, and white cell counts were normal in all the patients.

Twenty-one healthy individuals (11 males and 10 females), aged 20 to 49 (mean 27 ±7.4) years, served as controls. Three of the males were smokers.

Venous occlusion test. A detailed description of the venous occlusion test is given elsewhere (Petäjä 1989). Briefly, a sphygmomanometer cuff around the upper arm was inflated to a pressure midway between the systolic and the diastolic pressure and was maintained for 20 minutes. Blood samples were collected before stasis and during stasis after 20 minutes in the morning after rest. For citrated plasma samples (TPA antigen and PAI assays), nine volumes of blood were mixed with one volume of 0.129 M trisodium citrate. For TPA activity assay, two volumes of citrated blood were acidified with one volume of acetate buffer (1 M, pH 3.9).

Analytical methods. TPA and PAI activities were determined with Coa-Set TPA/PAI from KabiVitrum (Stockholm). TPA antigen (TPA:Ag) was measured by the ELISA method with Imulyse 5 TPA from Biopool AB, Umeå, Sweden. Packed cell volume was also measured, and a constant hemoconcentration was observed during venous occlusion. No difference was observed in hemoconcentration between the patients and the controls. Therefore, postocclusional values of TPA and PAI were not corrected for hemoconcentration. The fibrinolytic activity of TPA was expressed in international units (IU) and the activity of PAI in arbitrary units (AU). One arbitrary unit of PAI is equivalent to the inhibition of 1 IU of TPA during 10 minutes of incubation.

Statistics

The two-tailed *t*-test of the independent samples was used to test the difference between mean values. For postocclusional TPA activity and TPA:Ag, the Mann-Whitney *U*-test was used. Pearson's correlation test was also applied. $P < 0.05$ was considered significant.

Results

Basal TPA activity was decreased in the patients compared with the controls (1.8 ± 0.7 vs. 3.0 ± 1.4 IU/mL, $P < 0.001$) while the TPA:Ag level was increased ($P < 0.001$; Table 2). No difference was seen in basal PAI levels between patients and controls. After venous occlusion, there was no difference in TPA activity between the two groups, but the TPA:Ag level was increased in the patients ($P < 0.001$). In accordance with a high level of TPA:Ag, PAI was lower in patients than in controls after venous occlusion ($P < 0.0001$).

No difference was observed between the smokers and nonsmokers in the patients as regards the fibrino-

Table 2. Basal levels of TPA:Ag, TPA activity, and PAI and after 20 minutes of venous occlusion in controls and chronic low back pain patients

		Controls			Patients			
	Time	mean	*SD*	n	mean	*SD*	n	*P*
TPA:Ag (ng/mL)	0	5.3	*2.1*	21	12	*5.7*	13	< 0.001
	20	50	*16*	20	117	*54*	13	< 0.001
TPA (IU/mL)	0	3.0	*1.4*	20	1.8	*0.7*	20	< 0.001
	20	56	*26*	19	58	37	20	NS
PAI (AU/mL)	0	15	*3.4*	21	15	*7.7*	20	NS
	20	7.5	*4.3*	20	2.2	*3.0*	20	< 0.0001

lytic capacity. Severity of radiographic pathology (central or lateral spinal stenosis, scar tissue, or arachnoiditis) did not either have a significant correlation with basal or postocclusional TPA, TPA:Ag, or PAI.

Discussion

The TPA:Ag level is known to increase with age (Hashimoto et al. 1987). This probably explains the increased TPA:Ag in our patient series, because the mean age of our patients was higher than that of the controls (for socioeconomic reasons, we could not obtain age-matched controls). However, the age difference does not explain our finding of decreased TPA activity in the presence of the increased TPA:Ag level but normal PAI activity. The low ratio between TPA activity and TPA:Ag in our patients suggests a defective function of TPA, the exact mechanism of which remains unclear. However, our results confirm the findings of low basal fibrinolytic activity in patients with chronic low back pain.

Jayson et al. (1984) suggested, based on basal fibrinolytic activity, that patients with chronic low back pain have a fibrinolytic defect. However, it appears that physiologically intravascular fibrinolysis is activated by rapid release of TPA upon local or systemic stimulation, and it is only this stimulated release that can overcome the inhibitory effect of PAI (Hessel and Kluft, 1986). Therefore, to test whether or not there is a constitutional defect in the fibrinolytic system in chronic low back pain patients, fibrinolysis must be measured after stimulation. In our study, there was no difference in TPA activity after venous occlusion between the patients and the controls. The fact that the patients released more TPA:Ag after venous occlusion than the controls may be due to an age difference. Alternatively, it could be due to a compensatory phenomenon. Once the biologically active basal TPA level is low, synthesis of total plasminogen activator—including the biologically inactive part, and reflected by TPA:Ag—is increased. The high release of TPA:Ag was reflected by a greater consumption of PAI during venous occlusion in the patients. Over all, our study suggests that a constitutionally defective fibrinolytic capacity is rare in chronic low back pain patients.

We conclude from our study that chronic low back pain patients show low fibrinolytic activity in peripheral venous blood in basal conditions, but they do not have a defective fibrinolytic capacity when measured after stimulation. The low basal activity of TPA is probably secondary to ongoing vascular and soft-tissue damage in the spine. The other possibility is that this low basal activity reflects some other contributing factor in chronic low back pain syndrome, e.g., TPA is also regulated by physical activity (Williams et al. 1980), and lowered basal activity might reflect diminished physical activity. Even if this is the case, the measurement of fibrinolysis in chronic low back pain patients may have clinical worth in the follow-up of the clinical condition.

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