# Thrombosis after hip replacement

## Relationship to the fibrinolytic system

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Twenty-nine patients were operated on with the Charnley hip prosthesis. All the patients were given dextran 70 as thrombosis prophylaxis. Deep vein thrombosis (DVT) was diagnosed in 10 patients with the radioactive fibrinogen uptake test and phlebography. Variables of coagulation and fibrinolysis were studied before and after surgery. Tissue plasminogen activator (t-PA) activity in the plasma without venous occlusion decreased postoperatively, but there was no correlation with DVT. The t-PA activity in venous occlusion plasma was not reduced after surgery. Plasminogen activator inhibitor (PAI-1) levels were raised immediately postoperatively. There was a significant correlation between preoperative PAI-1 activity and development of postoperative DVT ($P<0.05$). Patients developing DVT had higher levels of PAI-1 postoperatively than patients not developing DVT. A defective fibrinolytic system, as defined by high PAI-1 activity, thus predisposed to postoperative DVT.

Reduced fibrinolytic activity increases the risk of spontaneous thrombosis, and it probably also plays a role in the development of postoperative thrombosis (Åberg and Nilsson 1978, Nilsson et al. 1983, Mellbring et al. 1984, Sue-Ling et al. 1987).

New knowledge and specific assays of fibrinolytic variables have increased the possibilities of investigating the underlying mechanism of the fibrinolytic response to surgery. Impairment of the fibrinolytic system is often due to changes in the external system, i.e., reduced synthesis or release of tissue plasminogen activator (t-PA) from the vessel wall, or increased inhibition of t-PA . The tissue plasminogen activator inhibitor (PAI-1) seems to play a central role in the regulation of the fibrinolysis after trauma (Kluft et al. 1985, D'Angelo et al. 1985). Data on plasma levels of t-PA and PAI-1, related to deep vein thrombosis after surgery, have been reported by Paramo et al. 1985 and Kluft et al. 1986.

The main purpose of this study was to test the hypothesis that a defective fibrinolytic system predisposes to DVT after orthopedic surgery.

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## Patients and methods

Total hip replacement with the original Charnley procedure was done in 29 patients, 15 women and 14 men, mean age 69 years (SD ±7.2). Two of the patients were operated on owing to rheumatoid arthritis, one owing to necrosis of the femoral head after a cervical fracture and 26 owing to arthrosis. One of the patients had a previous history of deep vein thrombosis. Epidural anesthesia was given to 20 patients and general anesthesia to 9 patients. Dextran 70 was given as thrombosis prophylaxis to all of the patients with 500 mL during operation, 500 mL within 12 hours postoperatively, and 500 mL on the first and third days after operation. There were no serious intraoperative or early postoperative complications. The mean duration of operation was 126 min (SD ± 13 min), and the mean blood loss was 1,398 mL (SD ±450).

Screening for deep vein thrombosis was done with the $^{125}$I-fibrinogen uptake test before the operation and daily for 2 weeks postoperatively (Kakkar et al. 1970). The first 10 cm close to the groin were not scanned because of interference from isotope-labeled material in the urinary bladder and operative hematoma in the hip region. A positive finding was confirmed with phlebography (Greitz 1954), and a clinical follow-up of thromboembolism was done 6 weeks postoperatively.

The venous occlusion test for 10 min and blood sampling were done in all the patients preoperatively 1 day

and 1 week postoperatively. Blood samples were taken from the cubital vein between 8 and 10 a.m. The blood was anticoagulated with one volume of 0.13 mol/L trisodium citrate to nine volumes of blood. Plasma was immediately separated by centrifugation, frozen within 10 min, and stored at –70°C.

The t-PA activity in the plasma was measured with a spectrophotometric method in the presence of polylysine, plasminogen, and the chromogenic substrate S-2251 after separation from inhibitor by adsorption on lysine-Sepharose (Gyzander et al 1984). The t-PA activity was also determined with a fibrin-plate method standardized with purified melanoma t-PA (from M. Rånby, Umeå) with a specific activity of approximately 250,000 U/mg, as compared with urokinase standard in a clot lysis assay (Norén et al 1975). t-PA antigen in plasma was measured by Imulyse t-PA antigen kit (Biopool AB, Umeå, Sweden). PAI-1 activity in plasma was measured according to Eriksson et al. 1988. The reference value for 40 normal individuals was 4.0 ± 2.8 U/mL. One unit of PAI-1 activity corresponded to the amount that inhibited 1 IU of single chain t-PA.

Antithrombin III, $\alpha_2$-antiplasmin, $\alpha_2$-macroglobulin and plasminogen were analysed with chromogenic substrate techniques (Abildgaard 1977, Teger-Nilsson 1977, Harpel 1976, Friberger 1980). Fibrinogen was assayed with a syneresis method (Koepke 1980). The activity methods were standardized with pooled plasma from 20 normal individuals.

To test for significant differences between DVT and non-DVT patients a non-parametric test, the two-tail Mann-Whitney U was used. The two-tail Wilcoxon signed rank test was used in the comparison of two groups in paired samples. $P < 0.05$ was considered significant. Pearson's coefficient of correlation was used in analysis of the relationship between the two methods of measuring t-PA activity.

## Results

Deep vein thrombosis (DVT) was found in 10 of 29 patients: calf vein thrombosis in 9, concomitant femoral thrombosis in 1, and isolated femoral thrombosis in 1 patient. One of these patients had a clinically evident nonfatal pulmonary embolism verified with perfusion scanning. There was no difference between epidural and general anesthesia in the frequency of deep vein thrombosis. One patient with previous thrombosis had a fresh thrombus in the same leg.

*t-PA activity in plasma, sampled without venous occlusion* (Table 1). The t-PA activity was reduced both 1 and 7 days after the operation as compared with preoperative values. The level of t-PA activity was lowest 1 day postoperatively and increased 1 week after the operation. There was a clear correlation between activity of tissue plasminogen activator measured by the chromogenic-substrate method and the fibrin-plate method ($r = 0.78$, $P < 0.001$). These assays of t-PA activity did not reveal any difference between patients who developed DVT and those who did not.

*PAI-1 activity in plasma, sampled without venous occlusion* (Table 2). Postoperative PAI-1 values were increased compared with preoperative values both 1 and 7 days after surgery. PAI-1 activity reached peak level 1 day postoperatively and was reduced 1 week after the operation. The preoperative PAI-1 level was higher in patients developing DVT compared with patients who did not develop DVT. This difference between DVT and non-DVT patients was also seen 1 week after surgery.

*t-PA antigen in plasma, sampled without venous occlusion* (Table 2). The first day after the operation, t-PA antigen increased significantly, and that level was maintained when measured after 1 week. Patients with postoperative DVT had higher t-PA antigen preoperatively compared with patients without DVT. The first postoperative day t-PA antigen was similar in both groups, but after 1 week, DVT patients had higher t-PA antigen than non-DVT patients.

*After venous occlusion* the t-PA activity in plasma increased 10 times compared with normal plasma in preoperative samples (Table 3, Table 1). There was no change postoperatively, and there was no difference between DVT and non-DVT patients. The individual variation was wide. The chromogenic-substrate method and the fibrin-plate method correlated well ($r = 0.92$, $P < 0.001$). The t-PA antigen and PAI-1 activity were not measured in stasis plasma.

*Plasminogen, $\alpha_2$-antiplasmin, $\alpha_2$-macroglobulin, fibrinogen and antithrombin III in pre-occlusion plasma* (Table 4). Plasminogen decreased one day

Tables 1. Tissue plasminogen activator activity in plasma (IU/mL) without venous occlusion (n 29). All values were corrected for changes in hematocrit. Mean *SD*

| Method | Preop. | Postop. | |
|---|---|---|---|
| | | 1 day | 7 days |
| | | * | |
| | | *** | * |
| Chromogen. substr. | 0.60 *0.33* | 0.25 *0.21* | 0.46 *0.30* |
| Fibrin plate | 0.62 *0.30* | 0.19 *0.17* | 0.46 *0.33* |

Correlation between t-PA activity measured by the chromogenic substrate method and the fibrin-plate method ($r = 0.78$, $P < 0.001$).

Table 2. PAI-1 activity and t-PA antigen in plasma without venous occlusion

| | | Preop. | | | 1 day postop. | | | 7 days postop. | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | DVT n 10 | NonDVT n 19 | Total n 29 | DVT n 10 | NonDVT n 19 | Total n 29 | DVT n 10 | NonDVT n 19 | Total n 29 |
| | | | | *** | | | ** | | | |
| | | | * | | | | | | * | |
| PAI-1 (U/ml) | Mean | 7.6 | 4.0 | 5.2 | 20.7 | 12.1 | 15.1 | 16.0 | 5.2 | 9.1 |
| | *SD* | *4.3* | *4.1* | *4.2* | *11.8* | *8.6* | *9.7* | *11.9* | *4.1* | *6.8* |
| | | | | *** | | | | | | |
| | | | * | | | | | | * | |
| t-PA antigen (ng/ml) | Mean | 10.9 | 8.3 | 9.4 | 14.4 | 13.2 | 13.6 | 18.8 | 12.1 | 14.2 |
| | *SD* | *2.9* | *2.0* | *2.6* | *5.3* | *4.1* | *4.6* | *8.4* | *3.0* | *6.6* |

PAI-1 activity (U/ml) and t-PA antigen (ng/ml) measured in plasma without venous occlusion all values were corrected for changes in hematocrit. * = $P < 0.05$, ** = $P < 0.01$, and *** = $P < 0.001$

Table 3. Tissue plasminogen activator activity (IU/mL) in venous occlusion plasma (n 29). All values were corrected for changes in hematocrit. Mean *SD*

| Method | Preop. | | Postop. 1 day | | Postop. 7 days | |
|---|---|---|---|---|---|---|
| Chromogen. substr. | 6.9 | *6.7* | 7.0 | *6.9* | 5.6 | *5.2* |
| Fibrin plate | 7.8 | *7.7* | 7.3 | *7.2* | 5.9 | *4.9* |

Correlation between t-PA activity measured by the chromogenic-substrate method and the fibrin-plate method ($r = 0.92$, $P < 0.001$).

after the operation and was increased 1 week postoperatively compared with preoperative values. The $a_2$-antiplasmin was unchanged the first postoperative day, and increased 1 week after the operation. In contrast, $a_2$-macroglobulin showed a decrease both 1 day and 1 week postoperatively. Fibrinogen followed the pattern of $a_2$-antiplasmin. Changes in Antithrombin III postoperatively were small, though significant. None of these variables correlated with DVT.

## Discussion

The mechanism of postoperative deep vein thrombosis (DVT) is complex. There is increasing evidence that impairment of the fibrinolytic system predisposes to thromboembolic disease. Impaired fibrinolytic capacity is an important etiologic factor in spontaneous thrombosis (Pandolfi et al. 1969, Nilsson et al. 1985, Wiman et al. 1985, Juhan-Vague et al. 1987). Following trauma, there is a fibrinolytic shut down within the first few postoperative days. The mechanism is not completely clarified, but a rapid postoperative increase of tissue plasminogen activator inhibitor (PAI-1) seems to be of importance (Kluft et al. 1985).

Mellbring et al. (1983) found that patients subjected to major abdominal surgery with increased fibrinolytic activity preoperatively were less prone to develop postoperative DVT. These findings were in agreement with other authors who reported a correlation between reduced fibrinolytic activity and postoperative thrombosis (Paramo et al. 1985, Sue-Ling et al. 1987). In contrast to these studies are reports where no correla-

Table 4. Fibrinolytic parameters in plasma without venous occlusion. All values were corrected for changes in hematocrit. Mean *SD*

| | Preop. n 29 | | 1 day postop. n 28 | | 7 days postop. n 29 | |
|---|---|---|---|---|---|---|
| Plasminogen (%) | 94.9 | *14.1* | 75.1 | *9.4* | 112 | *21.2* |
| $\alpha_2$-Antiplasmin (%) | 96.4 | *9.20* | 93.9 | *11.0* | 119 | *14.9* |
| $\alpha_2$-Macroglobulin (g/L) | 1.97 | *0.69* | 1.47 | *0.40* | 1.53 | *0.35* |
| Fibrinogen (g/L) | 3.11 | *0.68* | 3.06 | *0.51* | 5.14 | *1.01* |
| Antithrombin III (%) | 96.4 | *10.5* | 90.6 | *8.6* | 110 | *13.7* |

tion between fibrinolysis and postoperative thrombosis was found (Macintyre et al.1976, Reilly et al. 1980).

There are, however, reasons to reevaluate previous studies. New techniques for accurate measurement of t-PA, t-PA antigen, and PAI-1 have improved the understanding of fibrinolytic reactions. Contradictory reports on the relationship between fibrinolysis and postoperative thrombosis might also be due to different types of surgery. A difference in thrombogenic mechanism in abdominal versus orthopedic surgery has been suggested (Paramo et al. 1985, Kluft et a. 1986).

The main finding from the present study was that high preoperative PAI-1 predisposes to DVT. Further, DVT patients had significantly higher preoperative values of t-PA antigen. One week after the operation, levels of PAI-1 and t-PA antigen were higher in thrombosis patients. Thus, patients with defective fibrinolytic system were inclined to develop DVT. There was a fibrinolytic shutdown the first postoperative day, expressed as reduced t-PA activity and elevation of PAI-1 activity. t-PA antigen increased after surgery, and the increase was still evident 1 week after operation.

Not much is known about regulation of the synthesis and release of t-PA and PAI-1, but these findings could indicate that t-PA and PAI-1 are acute phase reactants. Kluft et al. (1985) verified this for PAI-1, which they found to be a very rapid acute-phase reactant. Regulation of t-PA release may, however, occur by different routes, and is probably related to endothelial cells. The increase of PAI-1 was more rapid and more pronounced than that of t-PA, causing the postoperative fibrinolytic shutdown. PAI-1 levels were raised immediately postoperatively. The low t-PA activity in spite of elevated t-PA antigen suggested that the fibrinolytic response to surgery, to a great extent, was determined by the inhibitor PAI-1 . This was also in accordance with other authors (D'Angelo et al. 1985, Mellbring et al. 1985). The very low t-PA activity after operation in plasma without venous occlusion could be due to an increased PAI-1 activity. This suggestion is supported by the fact that the t-PA activity in plasma after venous occlusion was unaffected by surgery, i.e., the t-PA content of the venous vessel wall was not depleted.

Dextran 70, as used in this study for thrombosis prophylaxis, could in itself affect the fibrinolytic activity. It was previously demonstrated that dextran reduced the postoperative fibrinolytic inhibition (Carlin and Saldeen 1979), and thus counteracted the fibrinolytic shutdown. This effect could be mediated by dextran-induced reduction in PAI-1 (Saldeen et al. 1987).

Plasminogen, $\alpha_2$-antiplasmin, and fibrinogen followed the pattern of acute-phase reactants. $\alpha_2$-macroglobulin showed a significant decrease both 1 day and 1 week postoperatively. There was no difference between thrombosis and nonthrombosis patients with respect to these plasma proteins.

Thrombosis was diagnosed in 10 of 29 patients (34 per cent). Only 1 patient, with a synovitis in the knee joint, had a positive $^{125}$I-fibrinogen test and negative phlebogram. The diagnostic methods of DVT after hip surgery could be disputed. The $^{125}$I-fibrinogen uptake test becomes positive in the presence of hematoma and interference from isotope-labeled material in the urinary bladder. DVT in the proximal femoral region could not be ruled out because of this. The incidence of isolated thrombi in the proximal thigh will determine the utility of the test. Following hip surgery, the occurrence of isolated proximal femoral thrombi, without concomitant thrombi in the lower leg, was found to be 6 percent by Nillius and Nylander (1979). From this it can be extrapolated that 1 or 2 patients with isolated DVT in the proximal thigh region could have been missed in the present study.

The main finding from this study on patients undergoing total hip replacement was that a defective fibrinolytic system is a predisposing factor of postoperative DVT.

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