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The Effects of Different Anesthetic Regimens on Fibrinolysis and the Development of Postoperative Arterial Thrombosis

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Background: **The purpose of this clinical trial was to compare the effects of different anesthetic and analgesic regimens on hemostatic function and postoperative arterial thrombotic complications.**

Methods: **Ninety-five patients scheduled for elective lower extremity vascular reconstruction were randomized to receive either epidural anesthesia followed by epidural fentanyl (RA) or general anesthesia followed by intravenous morphine (GA). Intraoperative and postoperative care were controlled by protocol using predetermined limits for heart rate, blood pressure, and other monitoring criteria. Data collection included serial physical examinations, electrocardiograms, and cardiac isoenzymes to detect arterial thrombosis (defined as unstable angina, myocardial infarction, or vascular graft occlusion requiring reoperation). Fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and D-dimer levels were measured preoperatively and at 24 and 72 h postoperatively.**

Results: **Preoperative fibrinogen levels were similar in both groups, remained unchanged after 24 h, and increased equally (45%) in the first 72 h postoperatively. PAI-1 levels in the GA group increased from 13.6 ± 2.1 activity units (AU)/ml to 20.2 ± 2.6 AU/ml at 24 h and returned to baseline at 72 h. In contrast, PAI-1 levels in the RA group remained unchanged over time. Twenty-two of 95 patients (23%) had postoperative arterial thrombosis, 17 of whom had received GA and 5 of whom, RA. Preoperative PAI-1 levels were higher in patients who developed postoperative arterial thrombosis (20.5 ± 3.6 AU/ml *vs.* 11.2 ± 1.4 AU/ml). Multiple logistic regression analysis indicated that GA and preoperative PAI-1 levels were predictive of postoperative arterial thrombotic complications.**

Conclusions: **Impaired fibrinolysis may be related causally to postoperative arterial thrombosis. Because RA combined with epidural fentanyl analgesia appears to prevent postoperative inhibition of fibrinolysis, this form of perioperative management may decrease the risk of arterial thrombotic complications in patients undergoing lower extremity revascularization. (Key words: Coagulation: D-dimer; fibrinogen; fibrinolysis thrombosis; plasminogen activator inhibitor-1. Heart: myocardial infarction.)**

PERIOPERATIVE changes in hemostasis have been hypothesized to explain the high frequency of deep venous thrombosis and pulmonary embolism after surgery.[1] Increased plasma concentrations of coagulation factors,[2] decreased concentrations of coagulation inhibitors,[3] enhanced *in vitro* platelet reactivity,[4] and impaired *in vitro* fibrinolysis[5] have been reported postoperatively, suggesting a "hypercoagulable state."

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Teleologically, an increased tendency for blood to coagulate after tissue trauma can be viewed as adaptive; however, in patients with stenotic coronary or peripheral vascular lesions, these hemostatic changes have the potential to increase the likelihood of arterial thrombotic complications *(i.e.,* unstable angina, myocardial infarction (MI), or limb loss).

In nonoperative settings, there is considerable evidence supporting an association between hemostatic changes and the development of coronary ischemic syndromes (unstable angina and non-Q wave and Q-wave MI). Elevated coagulation proteins,[6] increased platelet activation,[7] and decreased fibrinolysis[8] have been reported to be predictors of MI. Circadian increases in hemostasis coincide with the timing of coronary ischemic events,[9,10] and changes in platelet reactivity are temporally associated with the development of unstable angina.[11] Evidence linking postoperative hypercoagulability with arterial thrombotic complications was reported recently by Tuman *et al.*[12] The observed reduction in coronary ischemic syndromes and postoperative vascular graft occlusion in patients receiving anticoagulants[13,14,15] provides further support for any etiologic role of hypercoagulability in both of these events.

Investigators long have been interested in identifying anesthetic regimens that modulate the stress response to surgery. Regional anesthesia (RA) has been reported to reduce perioperative morbidity and mortality when compared with general anesthesia (GA).[16] Regional anesthesia has been shown also to decrease the incidence of postoperative deep venous thrombosis,[17] which has been attributed to increases in lower extremity blood flow and a reduced incidence of procoagulant effects. In support of this latter conclusion, RA has been shown to result in less inhibition of fibrinolysis[18] and smaller increases in coagulation factors than has GA.[19]

The comparative studies discussed above did not attempt to ensure that important (and controllable) parameters, such as blood pressure, heart rate, medications used, and postoperative analgesia, were not responsible for observed differences in hemostasis and outcome. The present study examines selected aspects of hemostasis in patients undergoing lower extremity revascularization randomized to different anesthetic/analgesic regimens. We hypothesized that perioperative changes in hemostasis contribute to development of arterial thrombosis in patients with predisposing arterial vascular lesions. All treatment decisions were based on predetermined protocols designed to achieve comparable control of blood pressure, heart rate, and pain relief both intraoperatively and during the first 24 h postoperatively. By controlling these variables, differences in hemostasis and thrombotic clinical events are ascribed more easily to intrinsic features of the anesthetic/analgesic technique.

Methods and Materials

This investigation was conducted on a subset of patients enrolled in a clinical trial designed to evaluate differences in perioperative morbidity and mortality between regional and general anesthesia.[20] Patients undergoing elective lower extremity revascularization for atherosclerotic peripheral vascular disease were studied. Patients were excluded from study if their procedures involved the iliac arteries or the aorta, if they had a contraindication to either epidural or GA (coagulopathy or significant upper airway abnormality), or if they had electrocardiographic (ECG) abnormalities that made ST segment analysis difficult (left bundle branch block or resting ST segment abnormalities because of left ventricular hypertrophy). Patients were identified from the surgery schedule, evaluated for eligibility, and approached for consent 1–3 days before surgery.

The evening before surgery, patients were stratified by both surgeon and degree of cardiac risk. Randomization was blocked within strata of variable sizes arranged in random order. Consenting patients were randomized immediately before surgery to receive either epidural or general anesthesia. Patients received their usual chronic medications, except for oral hypoglycemics, on the morning of surgery. All patients were premedicated with intramuscular midazolam (up to 5 mg) and morphine sulfate (0.1 mg/kg).

Patients receiving regional anesthesia first were administered an infusion of 10–15 ml/kg of lactated ringers. After identification of the epidural space (*via* L2–L3 or L3–L4 interspace), a test dose of 3 ml 0.75% bupivicaine with 1:200,000 epinephrine was instilled. Lumbar epidural anesthesia was initiated with 0.75% bupivicaine and titrated to maintain a sensory block at the T6–T8 level, assessed by patients' loss of sharp sensation to pinprick. Patients receiving epidural anesthesia received intravenous midazolam (in 0.5 mg increments) and fentanyl (in 25 μg increments) as needed to maintain sedation. During skin closure, patients re-

ceived a bolus of fentanyl (100 μg) in 10 ml sterile saline through the epidural catheter.

General anesthesia was induced with increments of thiamylal (50 mg) and fentanyl (25–50 μg). Ventilation first was assisted, then was controlled as unconsciousness supervened. A series of graded stimuli, including an oral airway, a urinary catheter, and tracheal instillation of lidocaine, were initiated to assess anesthetic depth. Increases of heart rate or blood pressure with these maneuvers were treated with additional fentanyl (up to 7 μg/kg) and thiamylal (up to 5 mg/kg). Succinylcholine (1 mg/kg) was administered intravenously to facilitate tracheal intubation. Anesthesia was maintained using enflurane (0.5%–1.0%) and nitrous oxide (50%) in oxygen. Pancuronium (0.05 mg/kg) was given intravenously immediately after induction. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide pressure at 35–40 mmHg. Incremental doses of morphine sulfate (1–2 mg) were administered intravenously during closure, with the dose titrated to maintain a respiratory rate of between 10 and 16 breaths per min and an end-tidal carbon dioxide pressure of between 45 mmHg and 55 mmHg. All patients were extubated before leaving the operating room and went to the Intensive Care Unit (ICU) for the first 18–24 h postoperatively.

Intraoperatively, all patients received an intravenous heparin bolus (approximately 70 units/kg) before clamping of the arterial vessel. A infusion of low molecular weight dextran (dextran 40) at 20 ml/h was administered to most patients during surgical closure and maintained for 18–24 h postoperatively. Postoperative pain management was provided in the RA group with continuous epidural fentanyl at 50 μg/h and in the GA group with IVPCA morphine at 0.5 mg/h with 1 mg bolus doses and 10 min lockout. Inadequate pain relief was treated by increasing the background rate and/or additional bolus doses in both the epidural and IVPCA groups. After discharge from the ICU, both groups received morphine intramuscularly as determined by the surgical team.

All patients were monitored intraoperatively with pulse oximetry, an ECG that included precordial V5, and an intraarterial catheter. The need for further invasive hemodynamic monitoring was determined before randomization by a protocol based on each patient's medical condition. Heart rate was maintained at 40–85 beats/min if the patient was in sinus rhythm, and at 40–100 beats/min if the patient was in atrial fibrillation. Blood pressure limits were based on the median of three preoperative blood pressures and a nomogram that yielded clinically rational pressures over a wide range.[20] These vital sign goals were used in the ICU postoperatively to guide fluid administration and adjustment of analgesics. Treatment with cardiovascular agents was instituted when necessary.

Blood was obtained for analysis of fibrinogen, PAI-1, and D-dimer before induction and at 24 h and 72 h postoperatively. The first two samples were obtained through an arterial line, and the third was obtained either by an arterial line, if the patient was still in the ICU, or by peripheral venipuncture, if the patient had been transferred to the ward. Blood was collected at the same time each day to prevent circadian effects. Blood samples were collected in citrated glass tubes, placed on ice, and centrifuged at 3,000 RPMs for 20 min. Plasma was removed and stored at −70° C until testing. Fibrinogen was assayed using the vonClauss method,[21] and results are reported in grams per liter (normal, 1.5–4.0 g/l). PAI-1 levels were measured using a chromogenic substrate method (Kabivitrum, Mölndal, Sweden) and reported in activity units (AU) per milliliter (1 AU is the amount of PAI-1 that inhibits 1 IU of tissue-type plasminogen activators, with the normal range being 5–15 AU/ml).# D-dimer determinations were made using a latex agglutination immunoassay (Organon, Teknika, Durham, NC).[22] This is a semiquantitative assay that measures the presence of D-dimers and quantitates the concentration at either less than 500 ng/ml (which is considered normal), 500–1,000 ng/ml, or greater than 1,000 ng/ml.

To correlate them with hemostatic parameters, arterial thrombotic events were defined as cardiac death, nonfatal myocardial infarction, unstable angina, and graft occlusion requiring reoperation. Types of reoperation included thrombectomy, revascularization, or amputation at the knee. Cardiac outcomes were determined by a cardiologist, blinded to the type of anesthetic used, on the basis of the following criteria: ECGs obtained the day before surgery, the day of surgery, and on postoperative days 1, 2, 3, and 7; creatinine phosphokinase and myelin B bands drawn at 6-h intervals during the ICU stay and daily through postoperative day 3; and information on chest pain during the first 7 postoperative days. The cardiologist also was given access to information from autopsy, death certificates,

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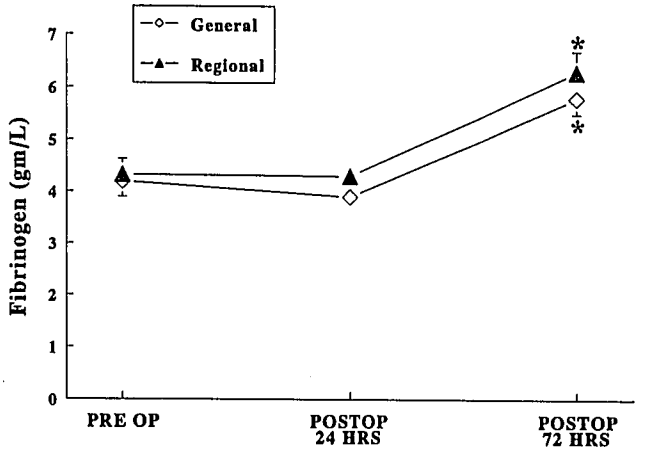

Fig. 1. Fibrinogen levels in grams/liter for general and regional anesthesia groups over time. Values are mean ± SEM. *$P <$ 0.001 compared to preop and 24 h postop.

and cardiology consultations after this information was screened to determine that it would not disclose the type of anesthetic used. The criteria of the Lipid Research Clinics** were used to diagnose cardiac death, myocardial infarction, and unstable angina. ECG abnormalities were diagnosed in accordance with the Minnesota Code.[23] Cardiac outcomes were based on results obtained throughout the first 7 postoperative days. Reoperation was determined by a review of the chart at the time the patient was discharged from the hospital. Graft occlusion was defined as thrombectomy or revascularization within 10 days of the original surgery or amputations within 14 days (with evidence of decreased distal perfusion within 10 days).

Statistical Analysis

Statistical analysis was performed using SPSS release 4.1 for IBM OS/MDS (SPSS, Chicago, IL). Discrete variables were analyzed using chi square and continuous variables by Student's *t* test. Multiple logistic regression analysis with backward elimination was used to adjust for baseline differences. The time course of continuous variables were analyzed using two-way analysis of variance for repeated measures. All reported *P* values are two-tailed and considered significant at the $P < 0.05$ level. All results are reported on the basis of treatment administered.

** The Lipid Research Clinics Program: The coronary primary prevention trial: Design and implementation. J Chron Dis 32:609–631, 1979.

Results

Type of Anesthesia/Analgesia

One hundred patients were enrolled in the study—51 were randomized to receive GA and 49, to receive RA. Five patients were not analyzed for coagulation—two patients (1 GA and 1 RA) who died within the first 24 h and three patients from whom blood samples were not obtained. Three patients randomized to RA received GA because the epidural could not be placed, and these patients were analyzed in the GA group. The groups were similar in age, gender, ASA classification, Goldman risk index, cardiac history, chronic medications, and severity of vascular disease.[20] Preoperative fibrinogen levels (fig. 1) were 4.02 ± 0.26 g/l and 4.33 ± 0.26 g/l in the GA and RA groups, respectively. There was no change in fibrinogen levels in either group at 24 h, but a 45% increase was observed in both groups at 72 h. Preoperative PAI-1 levels were 13.6 ± 2.1 AU/ml and 13.3 ± 1.9 AU/ml for GA and RA patients, respectively (fig. 2). PAI-1 levels in the RA patients did not change over time. In contrast, PAI-1 levels in patients receiving GA had a increased significantly at 24 h and returned to near preoperative levels at 72 h. Direct comparison indicated that PAI-1 levels behaved differently in the two anesthetic/analgesic groups. D-dimer results were similar with the two anesthesia/analgesia regimens and did not change over time.

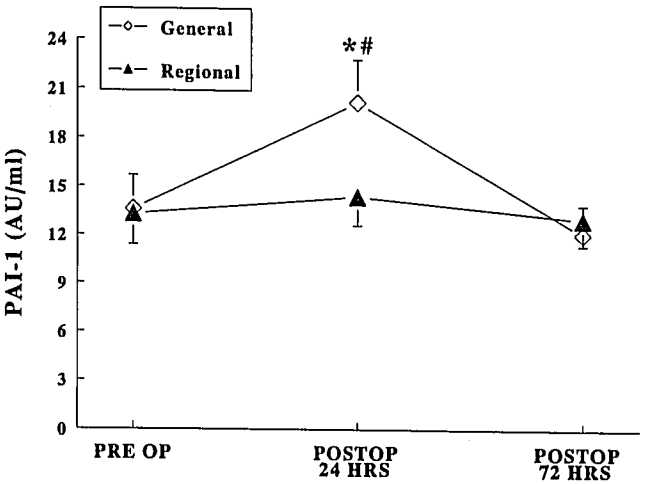

Fig. 2. Plasminogen activator inhibitor-1 levels in activity units/milliliter for general and regional anesthesia groups over time. Values are mean ± SEM. #$P <$ 0.001 compared to preop and 72 h. *P = 0.05 GA compared to RA.

Table 1. Timing of Postoperative Arterial Thrombotic Events

	Postoperative Day
Cardiac	
Myocardial infarction (n = 4)	0 (2 patients), 1, 2
Unstable angina (n = 2)	0, 1
Reoperation	
Thrombectomy or revascularization (n = 12)	0 (7 patients), 1, 2, 3, 8, 9
Amputation (n = 6)	3 (2 patients), 4, 5, 8, 14

Postoperative Arterial Thrombosis

There were 24 arterial thrombotic events in 22 patients (23%). These were nonfatal MI in 4 patients, unstable angina in 2 patients, return to the operating room for thrombectomy and/or revascularization in 12 patients, and amputation in 6 patients. Table 1 lists the timing of these postoperative events.

Baseline characteristics of patients with and without arterial thrombotic complications are shown in table 2. The groups were comparable with regard to age, sex, ASA classification, Goldman Risk Index, hypertension, previous MI, prior coronary artery bypass grafting, and use of β blockers, nitrates, or calcium channel blockers. Perioperative use of anticoagulants is listed in table 3. There was no observed effect of preoperative or postoperative anticoagulants on development of arterial thrombosis. Other treatment variables are listed in table 4. Neither the type of lower extremity revascularization procedure performed nor the surgeon performing the procedure affected outcome. Similarly, there were no differences in estimated operative blood loss, blood products administered, or perioperative hypotension between those patients who developed a thrombosis and those who did not. The anesthesia/analgesia regimen was a significant determinant of outcome ($P = 0.01$); 17 of 22 (77%) patients developing thrombosis received GA, and 5 of 22 (23%) received RA. PAI-1 levels (fig. 3) throughout the study period were different in patients with and without thrombosis ($P < 0.001$), which included higher preoperative PAI-1 levels in patients who developed thrombosis (20.5 ± 3.6 AU/ml *vs.* 11.2 ± 1.4 AU/ml). Fibrinogen levels were no different preoperatively or after 24 h and in-

Table 2. Patient Characteristics

	Thrombosis (n = 22)	No Thrombosis (n = 73)	P
Age (yr)	67 ± 2.6	64 ± 1.3	0.32
Sex			0.80
Male	12	42	
Female	10	31	
Weight (kg)	68 ± 16.7	73 ± 15.8	0.23
ASA physical status			0.60
2	4 (18)	8 (11)	
3	16 (73)	60 (82)	
4	2 (9)	5 (7)	
Smoking	5 (23)	28 (38)	0.18
Diabetes	10 (45.5)	23 (31)	0.23
Previous myocardial infarction	4 (18)	19 (26)	0.52
Previous coronary artery bypass graft	2 (9)	11 (15)	0.47
Hypertension	13 (59)	46 (63)	0.74
β-blockers	5 (23)	11 (15)	0.40
Nitrates	3 (14)	6 (8)	0.45
Ca^{2+} channel blockers	6 (27)	22 (31)	0.76

Values are mean ± SD. Values in parentheses are percentages.

Table 3. Perioperative Anticoagulant Therapy

	Thrombosis (n = 22)	No Thrombosis (n = 73)	P
Preoperative			
Heparin IV	1 (4.8)	4 (5.5)	0.86
NSAIDs	3 (15)	16 (22)	0.49
Coumadin	2 (9)	5 (6.8)	0.72
Persantine	1 (4.8)	10 (14)	0.26
Postoperative			
Dextran IV	16 (76)	59 (81)	0.64
Heparin IV	7 (32)	12 (16)	0.11

IV = intravenous; NSAIDs = nonsteroidal antiinflammatory drugs.
Values in parentheses are percentages.

Table 4. Treatment Characteristics

	Thrombosis (n = 22)	No Thrombosis (n = 73)	P
Surgical procedure			
Femoral-proximal	10 (46)	31 (42.5)	0.80
Femoral-popliteal	8 (36)	31 (42.5)	0.61
Femoral-distal	2 (9)	7 (9.6)	0.94
Other*	2 (9)	4 (5.4)	0.54
Blood administered (units)	0.41 ± 0.67	0.19 ± 0.57	0.18
Estimated blood loss (ml)	470 ± 689	458 ± 521	0.94
Hypotension SICU (h)	0.77 ± 1.5	0.81 ± 2.1	0.94
Type of anesthesia			0.01
General	17 (77)	35 (48)	
Regional	5 (23)	38 (52)	

Values are mean ± SD. Values in parentheses are percentages.
* Femoral-femoral bypass and popliteal artery aneurysm repair.
SICU = surgical intensive care unit.

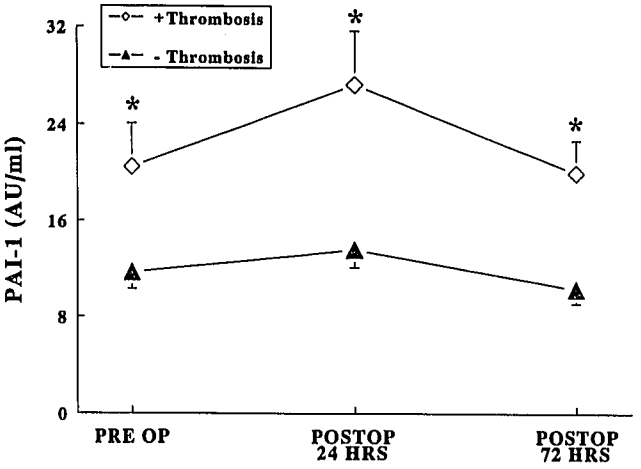

Fig. 3. Plasminogen activator inhibitor-1 levels in activity units/milliliter for (+) thrombosis and (−) no thrombosis groups over time. Values are mean ± SEM. *$P < 0.05$ vs no thrombosis.

creased to a similar degree in patients with and without thrombosis after 72 h. D-dimer levels also were no different in patients with and without thrombosis. Multiple logistic regression analysis demonstrated type of anesthesia ($P = 0.01$, odds ratio 4.70, 95% confidence intervals 1.45–15.21) and preoperative PAI-1 concentration ($P < 0.01$, odds ratio 1.05 per 1 AU/ml increase in PAI-1, 95% confidence intervals 1.01–1.08) to be the only variables predictive of postoperative arterial thrombosis.

Discussion

Patients undergoing peripheral vascular surgery commonly have a systemic vasculopathy that places them at high risk for developing coronary ischemic syndromes and lower extremity vascular occlusion. This study was undertaken originally to test the hypothesis that differential effects of anesthetic/analgesic regimens could alter postoperative hemostasis, causing coronary thrombosis. The development of lower extremity arterial thrombosis in the study population prompted expansion of the original hypothesis to include all arterial thrombotic events. We have demonstrated that PAI-1 levels increase postoperatively in patients who received GA and postoperative intravenous, patient-controlled analgesia morphine, but not in patients who received epidural anesthesia and postoperative continuous epidural fentanyl. We have demonstrated also that preoperative PAI-1 level and type of anesthesia/analgesia are predictive of postoperative arterial thrombosis, suggesting that impaired fibrinolysis may contribute to the development of these complications.

Type 1 PAI is a rapid and specific inhibitor of both tissue- and urokinase-type plasminogen activators (fig. 4); and may represent the primary regulator of plasminogen activation *in vivo*. Deficiencies of PAI-1 lead to excessive bleeding,[24] and elevated levels are associated with thrombosis.[25] PAI-1 is increased postoperatively in patients receiving GA and has been referred to as an acute phase protein.[5,26] However, PAI-1 levels did not rise in our patients receiving RA, and therefore probably is not a nonspecific acute phase protein. Furthermore, the failure of PAI-1 to rise in RA patients may explain previously reported differences in fibrinolysis between patients who have undergone either general or regional anesthesia. We hypothesize that early postoperative increases in circulating PAI-1 levels in GA patients may contribute to thrombosis within the first 48 h after surgery.

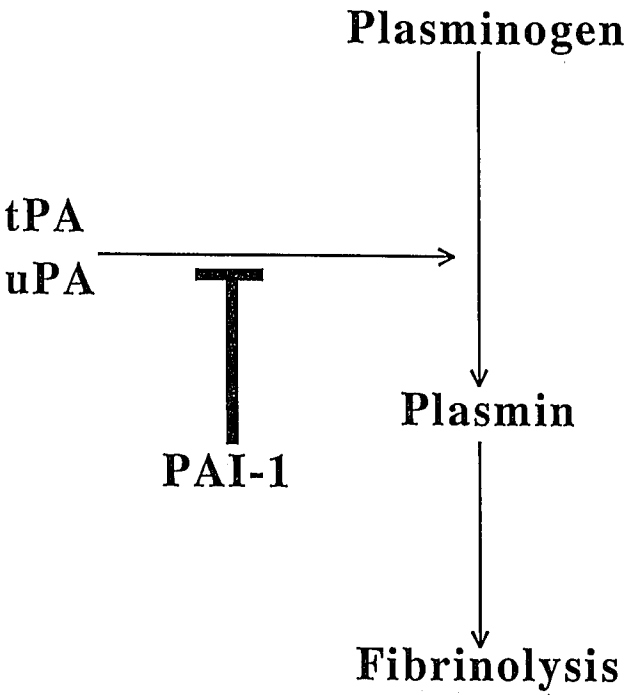

Fig. 4. A schematic summary of the fibrinolytic system. Both tissue and urokinase plasminogen activators (tPA and uPA) convert (→) plasminogen to plasmin promoting (→) fibrinolysis. Plasminogen activator inhibitor-1 blocks (—|) the activity of tPA and uPA.

Regional anesthesia attenuates the cortisol and catecholamine responses to surgery.[27] This attenuation has been suggested to be responsible for differences in hemostasis between regional and general anesthesia.[12,18] Experimental evidence supporting cortisol's effect on fibrinolysis comes from *in vitro* and *in vivo* studies demonstrating increased PAI-1 levels and impaired fibrinolysis found with dexamethasone administration.[28,29]

High preoperative PAI-1 levels were observed in our patients who developed postoperative thrombotic complications. This observation is consistent with previous studies demonstrating elevated PAI-1 levels in patients who develop spontaneous deep venous thrombosis,[30] postoperative deep venous thrombosis,[31] and MI.[32] PAI-1 levels also have been reported to be higher in patients with obesity,[33] diabetes mellitus,[34] and elevated triglyceride levels.[35] In our study, there were no differences in weight between those who had thrombosis and those who did not. In the group that developed thrombosis, a greater percentage of patients had diabetes than did not (45% *vs.* 31%), but this dissimilarity was not likely to account for the observed difference in PAI-1 levels. We did not measure triglyceride levels as part of this study. PAI-1 levels vary depending on the time of day,[9] and this circadian variation could be responsible for the difference between groups; however, surgical start times were the same in all groups, and postoperative samples were drawn at the same time of day that preoperative samples were obtained. It is possible that elevated preoperative PAI-1 levels represent a marker of more severe vascular disease, which would explain the association of elevated levels with postoperative arterial thrombosis. In support of this hypothesis, PAI-1 messenger RNA has been described in cells within atherosclerotic plaques,[36] and intracoronary thrombi contain high levels of PAI-1.[37] PAI-1 is released also from aggregating platelets,[38] which suggests that low level intravascular thrombosis may be occurring in patients with high PAI-1 levels before surgery. The increase in PAI-1 at 24 h and continued PAI-1 level elevation at 72 h observed in the group that developed thrombosis is consistent with the development of early and late postoperative arterial thrombosis.

Fibrinogen is a circulating glycoprotein produced by the liver, and elevated levels of this chemical are a marker for cardiovascular disease.[39] Fibrinogen association with cardiovascular risk may be related to the key role it plays in hemostasis. Fibrinogen is the precursor of fibrin and the plasma protein most responsible for plasma viscosity. Fibrinogen acts also as a ligand between activated glycoprotein IIb-IIIa receptor complexes on neighboring platelets, thus causing aggregation.[40] Fibrinogen is elevated postoperatively and typically is referred to as an acute phase protein.[2] Our data are in agreement with those of previous studies, demonstrating a postoperative increase in fibrinogen in all patient groups. In spite of fibrinogen's role as a marker for cardiovascular events in nonoperative settings, preoperative fibrinogen levels are not predictive of postoperative thrombosis. Furthermore, postoperative fibrinogen levels do not discriminate between patients with and without arterial thrombosis. It recently has been proposed that increases in the fibrinogen-platelet interaction are responsible for postoperative vascular insufficiency.[12] Our data suggest that enhanced fibrinogen binding to platelets may reflect expression of the glycoprotein IIb-IIIa receptor complex and is unrelated to fibrinogen level.

D-dimers are the end product of plasmin-cleaved, cross-linked fibrin, and elevated levels of it are indicative of fibrinolysis. A correlation between acute MI and elevated levels of D-dimers has been demonstrated previously.[41] We noted no perioperative or anesthetic-related difference in D-dimer levels, and they were not affected by the development of thrombosis.

The results of the present study suggest a reduced incidence of arterial thrombosis in patients who receive intraoperative epidural anesthesia followed by postoperative epidural fentanyl. However, we are unable to determine whether this effect is due to the intraoperative anesthetic or the postoperative analgesic regimen. A crossover study comparing both types of anesthesia with both analgesic regimens will be required to resolve this issue.

In summary, patients undergoing lower extremity revascularization are at risk for postoperative arterial thrombosis. Screening patients preoperatively for elevated PAI-1 levels may identify those patients who are at an increased risk for these postoperative events, which is associated with impaired fibrinolysis. RA with postoperative epidural fentanyl blocks the postoperative impairment in fibrinolysis seen with GA and postoperative intravenous, patient-controlled analgesia morphine. Further study into the role of fibrinolysis in postoperative arterial thrombosis and the effects of anesthetic and analgesic regimens on this condition are needed.

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