HAEMOSTATIC ACTIVATION
AFTER SURGERY AND TRAUMA
Relationship to clinicopathological findings

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Denne afhandling er i forbindelse med nedenstående publicerede afhandlinger af Det Sundhedsviden-skabelige Fakultet ved Aarhus Universitet antaget til offentlig at forsvares for den medicinske doktorgrad.


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dekan

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:


Preface

The work on which this thesis is based was conducted in the period from 1989 to 1994. It was performed while working with the Venous Thrombosis Group at the Department of Orthopaedics at Aalborg Hospital.

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Abbreviations

AMCA Tranexamic acid (Trans-4 aminomethylcyclohexanecarboxylic acid)
APTT Activate Partial Thromboplastin Test
ARDS Adult Respiratory Distress Syndrome
AT III Antithrombin III
BAL Bronchoalveolar lavage fluid
Boll-42 Fibrin/Fibrinogen degradation product derived from the ß chain
Boll5-42 Fibrin/Fibrinogen degradation product derived from the ß chain
CV Coefficient of Variation
D-dimer Fibrin Degradation Product of cross-linked fibrin (two D-domains)
DIC Disseminated Intravascular Coagulation
DVT Deep Vein Thrombosis
EACA Epsilon-aminocaproic acid
ECLT Euglobulin Clot Lysis Time
ELISA Enzyme-Linked Immunosorbent Assay
EPI Extrinsic Pathway Inhibitor
FbDP Fibrin Degradation Products
FDP Fibrin/Fibrinogen Degradation Products
FgDP Fibrinogen Degradation Products
FM Fibrin Monomers
FpA Fibrinopeptide A
F1+2 Prothrombin Fragment 1 and 2
GCS Glasgow Coma Scale
HC II Heparin Cofactor II
ISS Injury Severity Score
PAI Plasminogen Activator Inhibitor
PAI-1 Plasminogen Activator Inhibitor type 1
PAI-1:ag Plasminogen Activator Inhibitor type 1 antigen
PaO2 Arterial partial oxygen saturation
PC Protein C
PD Pulmonary Dysfunction
RIA Radioimmunoassay
RT Recalcification Time
TAT Thrombin/antithrombin III complex
TDP Total Degradation Products of fibrin and fibrinogen
THR Total Hip Replacement
t-PA Tissue Plasminogen Activator
t-PA:ag Tissue Plasminogen Activator antigen
XL-FDP Cross-linked Fibrin Degradation Products
1 Introduction

The soluble fibrinogen molecule may, with adequate stimulus, become insoluble in the blood and aggregate into fibrin complexes, which may be incorporated into larger fibrin clots. The haemostatic action of fibrinogen and platelets is an important factor in the prevention of deleterious and life-threatening loss of blood after trauma. Apart from the indispensable capacity to facilitate haemostasis, the fibrin network within the wound provides a physiological framework on which the process of wound healing can begin (1). On the other hand, when fibrin is deposited elsewhere, potentially harmful injury may occur due either to vascular obstruction or to initiation of inflammation and repair.

It has been suggested that the processes of the haemostatic system are controlled in a dynamic balance with the capacity to initiate repair of vascular lesions without interfering with the patency of the vascular tree (2,3). Events which activate the haemostatic system may therefore affect this balance. Haemostatic imbalance may occur when one or more controlling systems are overwhelmed or exhausted.

The alteration of blood coagulability in relation to haemorrhage was studied by William Hewson in 1772. He observed that “The blood taken later coagulated in less and less time till the blood issued last coagulated first” (4). In 1914, Gray and Lunt observed that the coagulation time of the blood decreased after experimental haemorrhage (5). In 1945, Bergquist made similar observations on patients during the early postoperative phase. The fall in whole blood coagulation time returned to normal in 24 to 48 h after operation (6). On the other hand, Macfarlane and Biggs found alterations in blood clot lysis time in connection with operation (7). It became evident that operation and trauma influenced several clotting and clot lysis-based haemostatic assays, but Warren et al wrote in 1950 that “We are obliged to state that throughout this work we have been conscious of the inadequacies of the methods used due to the lack of ability to isolate, with the exception of fibrinogen and platelets, the substances in question” (8). Until very recently quantification of the activation in the haemostatic system has been attempted by measurements of zymogens of the coagulation cascade (factors X, VIII, V, prothrombin, and fibrinogen). But they proved to be rather insensitive in the detection of haemostatic activation, possibly due to the fact that they are present in plasma in excess and only a minor fraction is activated or consumed during the haemostatic activation (9,10).

The recent development of immunochemical methods has made it possible to construct assays that can quantify the activities of various steps of the haemostatic system (9,10). The present study attempts to describe the influence of surgery, fractures of the extremities, neurotrauma, and multiple trauma on the generation of specific molecular markers of coagulation and fibrinolysis by newly developed immunochemical assays. Furthermore, it attempts to evaluate possible relationships between clinicopathological findings after surgery and trauma and the haemostatic activation.

2 Markers of haemostatic activation

2.1 Introduction

The enzymes generated during the coagulation and fibrinolysis cascades are not directly available for quantification. Several molecules that are released as a consequence of the enzymatic activation of thrombin and its action on fibrinogen can be quantified by immunological methods. Furthermore, the activation pathway for plasminogen, as well as the enzymatic reaction of plasmin on fibrin and fibrinogen, can be quantified. The processes that take place immediately before the formation of fibrin, and the processes that take place when fibrin is degraded, may then be characterized. Figure 1 presents a simplified scheme of the central actions in the formation and degradation of fibrin.

2.2 Prothrombin fragment 1+2 (F1+2)

Several pathways have been suggested for the conversion of prothrombin to thrombin, but under physiological conditions this process occurs in the presence of factor Xa, Va, and calcium ions, facilitating cleavage of prothrombin and liberation of thrombin and F1+2, which is a polypeptide of 273 amino acids (11) (Fig. 1). A double-antibody liquid-phase radioimmunoassay (RIA) for the determination of F1+2 was described in 1979 by Lau et al (12). Later, the same group evaluated the assay on clinical samples (13, 15). The plasma half-life of F1+2 was calculated as approximately 90 min in healthy individuals (14). Plasma levels of F1+2 increase with age (15). A two-site solid-phase immunoenzymatic assay is now available (16). In this assay the first antibody directed against F1+2 is immunoaffinity purified, while the second tagging peroxidase-conjugated antibody is polyclonal and directed against prothrombin. The enzyme activity on a chromogenic substrate is determined photometrically. In the original assay for F1+2 a special anticoagulant solution with protease inhibitors was recommended in order to prevent in vitro formation of F1+2 (12,13). Citrated plasma is recommended for the commercially available assay (16). The use of the thrombin inhibitor D-Phe-Pro-Arg-Chloromethylketone (p-pack) in clinical samples did not result in a reduction in levels of F1+2, TAT, FgDP, or FbDP, compared with levels in citrated plasma (17). The ELISA test was used in the present study for the
determination of F1+2 (Behring, Marburg, Germany) (16). The reference range given by the manufacturer is 0.44 - 1.11 nM between the 5th - 95th percentile. For 10-fold determination in one assay at two levels, the CV was 5.4% for 0.89 nM and 10.5% for 8.2 nM. The CV between series on test plasma was 14% for 0.51 nM on 5 occasions. Median (total range) in a group of 10 healthy individuals was 0.7 (0.3-1.8) nM.

2.3 Thrombin-antithrombin III complex (TAT)
Thrombin is inactivated by its main physiological inhibitor, antithrombin III, by irreversible complex formation (Fig. 1). In an experimental study, data indicated that TAT is cleared from plasma by a receptor-mediated mechanism on hepatocytes (18). The plasma half-life of TAT in animals is reported to vary between a few minutes to 11 h, depending on the experimental model used (18).

In 1980, Lau et al introduced a RIA for the determination of TAT, based on the double-antibody method in liquid-phase, as for F1+2 (19). A solid-phase two-site immunoenzymatic method is now available. A polyclonal antibody specific for thrombin binds the complex, and a second enzyme-labelled antibody against antithrombin is used to quantify the complex (20). The assay was evaluated on clinical samples; raised levels were observed in patients with thromboembolism and disseminated intravascular coagulation (DIC) (21).

In the present study, TAT was determined by the ELISA test (Behring, Marburg, Germany) (20). The reference range given by the manufacturer is 1.0 - 4.1 ng/ml between the 5th - 95th percentile. For 10-fold determination in one assay at two levels, the CV was 10.5% for 3.4 ng/ml and 10.7% for 43.7 ng/ml. The CV between series on test plasma was 9% for 10 ng/ml on 11 occasions. Median (total range) in a group of 10 healthy individuals was 1.7 (1.2-2.6) ng/ml.

2.4 Fibrinopeptide A (FpA)
In 1971, a RIA was introduced by Nossel and co-workers for the determination of FpA (22). FpA is a peptide of 16 amino acids cleaved from the Aα chain of the fibrinogen molecule by thrombin action (Fig. 1). The assay was later evaluated on clinical blood samples, and the disappearance rate from plasma in normal individuals was estimated to correspond to a plasma half-life of 3-5 min (23).

Several patient groups had increased levels of FpA in plasma, and it was observed that the in vitro generation of FpA was increased in certain patients, suggesting increased intravascular coagulation (24). To counteract erroneously raised levels of FpA due to in vitro generation, samples were processed in an anticoagulant solution of trasyrol and heparin (23,24). Since the antibodies used in the assay were not totally specific for FpA, depletion of fibrinogen prior to assay was necessary (23).

The FpA assay has been widely adopted as a very sensitive marker of coagulation activation, and very many studies concerning FpA have been published (25). However, the assay has not gained widespread clinical applicability due to cumbersome sampling technique and time-consuming assay procedures. It has been suggested that determination of FpA in the urine is a valid and sensitive method for the detection of the cumulative effect of thrombin action on fibrinogen. The recovery, stability, and accuracy have been reported as adequate (26-28). Increased urinary FpA immunoreactivity has been observed after myocardial infarction, ischaemic heart disease, peripheral artery disease, aortic aneurysm, malignancy, burn injury, and pulmonary embolism (26,27,29,30).

An ELISA test for the detection of FpA in fibrinogen depleted plasma was developed in 1980 (31). Polyclonal FpA antibodies are incubated in excess with the fibrinogen depleted plasma, and the incubation mixture is transferred to FpA-coated vessels. For further incubation, a second peroxidase conjugated anti-IgG antibody is added. The peroxidase reaction through (H2O2) on ortho-phenylenediamine is measured spectrophotometrically at 492 nm.

In the present study, FpA assay was performed with the ELISA test (31) (Boehringer Mannheim, GmbH, Diagnostica, Germany) on plasma depleted of fibrinogen by bentonite. The plasma was processed in an anticoagulant solution of citrate, trasyrol, and heparin. The reference range given by the manufacturer was <3 ng/ml. For 10-fold determination in one assay at two levels the CV was 8.6% for 2.1 ng/ml and 19.4% for 20.9 ng/ml. All levels in a group of 10 healthy individuals were below 3 ng/ml.

2.5 Fibrin monomers (FM)
Thrombin action on the fibrinogen molecule results in the formation of FpA, fibrinopeptide B, and soluble fibrin monomers (FM) (Fig. 1). Fibrin monomers may polymerize in plasma, and activated factor XIII catalyzes the cross-linking of fibrin polymers, resulting in precipitation from plasma of an insoluble network of fibrin.

Assays for the detection of soluble fibrin monomers have been available for more than 2 decades. They are qualitative tests based on gelatination of fibrin monomers by either ethanol or protamine sulphate (32,33). These tests are quickly and easily performed and have become widespread in clinical laboratories. A new assay for the determination of soluble FM was introduced by Wiman and Rånby in 1986 (34). This assay is based on the stimulatory effect of soluble fibrin on tissue plasminogen activator activation of plasminogen. The formed plasmin is quantified with a chromogenic substrate. The assay has been evaluated in laboratory and clinical studies by Halvorsen et al (35-37). They found good agreement between the FM test and other qualitative FM tests, but correlation between the FM test and the FpA
assay was poor, and it was suggested that fibrinogen interfered with the assay (35-37). FM was determined by this test (Diagnostica Kabi, Stockholm, Sweden). The sensitivity of the FM assay was 30 nmol/l, but it was improved by following the time-course of the increase of absorbance at 405nm and then plotting the second time derivative of A (d²A/dt²) against the linear-phase reaction (0.1<A <1.0) (34). By this modification the sensitivity of the assay was 3 nmol/l. For 10-fold determination in one assay at two levels the CV was 25% for 8 nmol/l and 3.7% for 131 nmol/l. Median (range) in a group of 10 healthy individuals was 4 (<3-19) nmol/l.

2.6 Fibrin/fibrinogen degradation products (FbDP, FgDP)

The degradation by plasmin of fibrinogen, soluble fibrin, and cross-linked fibrin results in a variety of degradation products, of which some can be further cleaved into smaller fragments (38). Semi-quantitative agglutination tests for the determination FbDP/FgDP appeared in the 1960s, and a polyclonal-based enzyme immunoassay for the detection of fibrinogen fragment E was developed in 1973 (39-41). Since the antibodies used in these assays cross-react virtually completely with fibrinogen, only serum samples could be used. However, artefactual results on serum samples have been demonstrated in samples containing heparin or anticoagulants (38). Semiquantitative agglutination tests for the determination of fibrinogen fragments are still used for clinical purposes. In the present study, the sensitivity of the FgDP assay was improved by following the time-course of the increase of absorbance at 405nm and then plotting the second time derivative of A (d²A/dt²) against the linear-phase reaction (0.1<A <1.0) (34). By this modification the sensitivity of the assay was 3 nmol/l. For 10-fold determination in one assay at two levels the CV was 25% for 8 nmol/l and 3.7% for 131 nmol/l. Median (range) in a group of 10 healthy individuals was 4 (<3-19) nmol/l.

2.7 Tissue plasminogen activator (t-PA)

Tissue plasminogen activator (t-PA) is a single-chain glycoprotein of 530 amino acids, which is synthesized by the endothelial cells. In the presence of plasminogen activator, plasminogen is converted to plasmin, which is quantified by reaction on a chromogenic substrate (54). The commercially available kit used for t-PA activity is from Chromogenix AB, Sweden (CoatestR PAI-1). In 44 healthy individuals, the manufacturer gives the median (range) as 6.0 ng/ml (1.7-18.4). In the present study, median (total range) in 10 healthy individuals was 4 ng/ml (1-8 ng/ml). For 9-fold determination in one assay at two levels, the CV was 4.7% for 4.6 ng/ml and 5.4% for 14 ng/ml.

2.8 Tissue plasminogen activator inhibitor type 1 (PAI-1)

Plasminogen activator inhibitor type 1 (PAI-1) is the principal inhibitor of t-PA. In the blood PAI-1 occurs in an active form, a latent form or bound to plasminogen activators. Platelets and plasma are distinct compartments for PAI-1 (53). As a consequence of considerable diurnal variation of PAI activity, the blood collection time should be standardized. Assays for the quantification of PAI activity are performed in principle by incubating samples with t-PA in excess. In the next step and in the presence of a stimulator (fibrinogen fragments), the residual t-PA activity activates plasmin, which is quantified by reaction on a chromogenic substrate (54). The PAI activity kit was supplied by Chromogenix AB, Sweden (CoatesR). In 44 healthy individuals, the manufacturer gives the median (range) as 3.9 AU/mL (0-71 AU/ml). For 10-fold
3 Alterations in haemostatic tests after surgery and trauma

3.1 Introduction
Tissue injury after trauma differs from that after surgery with respect to the absence of anaesthesia, often severe haemorrhage and traumatic shock or closed wounds, such as closed fractures, closed head injuries, and major soft tissue injury. Studies of haemostatic tests on surgical and trauma patients have been performed in the past. This chapter includes a survey of the literature and a presentation of the author's experience concerning alterations in haemostatic tests after surgery and trauma.

3.2 Intraoperative alterations in haemostatic tests
Shortening of clotting time, as determined by various clotting assays, has been observed during operations (55-58), but prolongation of the activated partial thromboplastin time assay (APTT) has been observed at the end of surgery (59). In hip surgery, Modig and Malmberg observed that the decrease in clotting time was most pronounced during insertion of the femoral component (60). Shortening of various global fibrinolytic tests has also been seen during surgery (57,61-63). Giercksky et al studied circulating tissue thromboplastin in 7 patients during hip surgery.
Samples taken during the operation contained measurable levels of tissue thromboplastin, whereas preoperative samples did not (64). A significant fall in antithrombin III (ATIII) activity has been observed under different surgical procedures (65,66). Sandset et al measured the activity levels of extrinsic pathway inhibitor (EPI), ATIII, heparin cofactor II (HCII), and protein C (PC) in hip surgery and cholecystectomy. Levels of all the coagulation inhibitors decreased during surgery. The underlying mechanisms were probably haemodilution, since plasma levels of albumin decreased accordingly (67).

In two studies on hip surgery, levels of FpA increased significantly at the time of inserting the femoral component (68,69). In the latter study a similar increase in levels of XL-FDP (cross-linked fibrin degradation products) was observed. In two other studies on hip surgery patients, levels of TAT increased by a factor of 10 during bone manipulation (70), and levels of F1+2 increased by a factor of 2 at the time of implementation of the acetabular component (71).

Increased haemostatic activation, as indicated by high levels of FpA, B15-42 (fibrinogen fragment), D-dimer (cross-linked fibrin degradation product), and TAT has been observed during gastric and hepatic surgery (72,73). Increased levels of t-PA activity, PAI activity, and PAI antigen have been found during hip surgery (71,74).

3.3 Postoperative coagulation tests

Shortening of coagulation time of the blood has been observed in the immediate postoperative period (6,56). A prolongation of the APTT has been reported in the postoperative period after abdominal surgery (75), but this was not seen in another study on general surgery patients (57).

Decreased levels of factor VII, prothrombin, fibrinogen, and platelets are usually seen in the immediate postoperative period after major surgery. From the first postoperative day a continuing rise is observed in levels of prothrombin, fibrinogen, platelets, factor VIII activity (VIII:C), and factor V activity. Levels become significantly higher than preoperative levels between the 3rd and 5th postoperative days (8,76-78) (I). The exact duration of this phase is at present unclear, but levels are still raised on the 10th postoperative day after major surgery. Observations have been made that AT III levels after major surgery return to preoperative levels within the 5th and 7th postoperative day (67,79) (Fig. 2). Similar observations have been made for EPI, HCII, and PC after hip surgery (67).

Increased levels of FpA have been reported after major abdominal surgery (80-82) and after major neurosurgical operations (83,84), but levels of FpA were not increased in the postoperative period after abdominal surgery in another study (75).

On the first postoperative day after hip surgery, levels of FpA were not increased over preoperative levels (69,85). However, on the 7th postoperative day FpA levels were significantly higher than preoperative levels (85). These observations on FpA levels are similar to the observations on F1+2 levels after hip surgery (II). In patients not receiving anticoagulants for thromboprophylaxis, postoperative levels of F1+2 were significantly higher than preoperative levels on days 3,5, and 7, but not on day 1 (II) (Fig.3). These observations on FpA and F1+2 may suggest a delayed reactivation of coagulation in the postoperative period. On the other hand, levels of TAT are highest on the first postoperative day and decrease gradually towards lower levels in the postoperative period (86-88) (I) (Fig.4). Similar observations on TAT were made after lung cancer surgery and upper abdominal surgery (82,89). These apparently contradictory observations may suggest that the plasma half-life of F1+2 and FpA is considerably shorter than the plasma half-life of TAT in the postoperative/traumatic period (see 3.6 and 3.7).

3.4 Postoperative fibrinolytic tests

Postoperative prolongation of global fibrinolytic tests has been observed (57,62,77,90-94). Conflicting results were observed in different patient groups, since global fibrinolytic tests indicated fibrinolytic shutdown in cancer patients undergoing surgery, but not in patients undergoing surgery for benign diseases (95). In a study using the euglobulin fraction on a fibrin plate, a decrease in activity from the first to the 7th postoperative day was observed (76). Other authors who used global fibrinolytic tests depending on fibrin digestion methods did not observe a postoperative fibrinolytic shutdown (96,97).

It was later suggested that the apparent postoperative reduction in fibrinolysis, as determined in the euglobulin fraction, was due to reduced t-PA activity, possibly as a consequence of increased PAI activity in the circulation (94,98-103). t-PA activity 24 h postoperative was significantly lower than preoperative activity. The t-PA activity increases on the following days, and it is significantly higher than preoperative levels on day 7. t-PA:ag levels were significantly higher than preoperative levels on the first, 5th, and 7th postoperative days (103). In accordance with these observations it is found that PAI-1 activity and PAI antigen are significantly higher than preoperative values on the first postoperative day. On the following days the PAI activity declines towards preoperative values, whereas PAI antigen levels remain higher than preoperative levels (102).

Levels of fibrinogen/fibrin degradation products are an indication of previous plasmin activity (104). B42 or B315-42 are such peptides released from plasmin action on fibrinogen and fibrin. These peptides, which have been quantified in several studies in the postoperative period, are reported to be significantly raised on the first postoperative day, followed by a continuing rise during the first 7 postoperative days (80,85,105). Similar results are obtained when tests
performed by monoclonal antibodies against fibrin degradation fragments are used (69,87,106) (II). In the author's study on hip surgery patients, levels of TDP increased during the entire study period, with highest levels on day 7 (II). The finding of increased levels of FDP in the postoperative period has led several authors to conclude that a period of postoperative fibrinolytic shutdown does not exist, since the occurrence of increased levels of FDP is an expression of enhanced plasmin activity in the circulation rather than reduced plasmin activity (80,85,105) (see 3.7).

No studies are yet available which have addressed the duration of the elevation of the haemostatic markers after surgery.

3.5 The effect of anaesthesia on haemostatic tests
After induction of general anaesthesia and before surgery, a significant decrease has been observed in levels of fibrinogen, AT III, prekallekrein, α-2-antiplasmin, and plasminogen (107). In another study, a slight decrease in factor VIII:C was observed after induction of general anaesthesia, and epidural anaesthesia produced a decrease in prothrombin levels. However, levels of fibrinogen, AT III, FDP, and streptokinase lysis time did not change after induction of either general or epidural anaesthesia (77). A slight decrease in levels of EPI, HC II, AT III, and PC is seen after induction of general anaesthesia, but infusions of crystalloids were started prior to the induction of anaesthesia (67). The global fibrinolytic test ECLT did not change after induction of general anaesthesia (63,72)). 4 out of 6 patients who had general anaesthesia had detectable levels of tissue thromboplastin after induction of anaesthesia, whereas only 1 patient had detectable levels prior to anaesthesia (64). FpA and XL-FDP did not change after the induction of general anaesthesia in patients scheduled for hip surgery (69). FpA levels remained unchanged after induction of anaesthesia in patients scheduled for abdominal surgery (72,108).

In several studies, patients have been randomly allocated to either general or epidural anaesthesia for surgery (59,77,108,109). Patients allocated to general anaesthesia had significantly higher values of serum fibrinolysis inhibition activity and factor VIII:C in the postoperative period than the patients allocated to epidural anaesthesia (109). Similar results concerning VIII:C were observed in other studies (108,110). Other authors have been unable to find differences between patients who had either general or epidural anaesthesia with respect to levels of coagulation factors, coagulation inhibitors, or global coagulation and fibrinolytic tests (59,77,111). No differences in levels of FpA were observed in patients randomized to either general or epidural anaesthesia (108). In another study, 36 patients were randomized to receive 6 different anaesthetic agents for abdominal hysterectomy, and it was observed that trichlorethylene and extradural anaesthesia caused a more pronounced shortening of the ECLT than other anaesthetic agents, but levels of serum FDP were unaffected by the type

![FIGURE 2. Antithrombin III activity levels in 28 patients who had no pharmacological thromboprophylaxis in the perioperative period after elective total hip replacement. (Data not previously](image)

![FIGURE 3. F1+2 levels in 62 patients who had no pharmacological thromboprophylaxis in the perioperative period after elective total hip replacement. (Paper II).](image)

![FIGURE 4. TAT levels in 33 patients who had no pharmacological thromboprophylaxis in the perioperative period after elective total hip replacement (Paper I).](image)
3.6 Haemostatic tests after isolated fractures of the lower limbs
Several earlier studies have attempted to estimate coagulation changes in patients with fractures of the lower limbs. However, it is not easy to derive much useful information from them (112,113). One study concluded that trauma which caused isolated fractures did not affect coagulation activity (114). Innes and Sevitt gave no specific information about coagulation changes in patients with isolated fractures of the lower limbs, but they stated that the changes were less pronounced than in patients with severe trauma (115).

In the author's study on patients with an isolated lower limb fracture (III), substantial haemostatic activation was observed, as indicated by high levels of F1+2, TAT, FM, FbDP, and FgDP shortly after trauma. At admission the correlations between the different coagulation markers were relatively strong, but on day 1 the correlations were weak or absent. An explanation for this observation could be that admission plasma levels reflect an equally increased production of the different markers, whereas on day 1 the plasma levels are the result of different degradation and excretion rates (III). The plasma levels of TAT, FbDP, and FgDP during the first week in patients with hip fractures are shown in figure 5. TAT levels decreased gradually in this period. Levels of FbDP and FgDP decreased from admission to day 3, but an increase between days 3 and 6 was observed, which was significant at the 5% level for both markers.
3.7 Haemostatic tests after multiple trauma and after isolated closed head injury

In the study performed by Innes and Sevitt in 1964, serial blood samples were taken from trauma victims in the posttraumatic period (115). Minor haemostatic disturbances were seen in patients who had isolated fractures of the extremities, whereas patients with multiple trauma had shortening of clot lysis time and clotting time in the first hours after trauma. Prolongation of the clot lysis time, together with a normal clotting time, occurred during the first posttraumatic day. Prolongation of both global tests continued on the following posttraumatic days. Coagulation factors, such as factor VII, factor V, prothrombin, and fibrinogen, were low shortly after trauma, but they increased to normal levels during the early posttraumatic period. Platelet count declined during the first 1-3 posttraumatic days, followed by thrombocytosis, which remained for more than a week. These findings were later confirmed by other authors who furthermore found raised levels of serum FDP in patients with multiple trauma or isolated head injury (114,116-120).

High levels of FpA have been observed in admission blood samples from patients with multiple trauma or head injury (121-123) (V). On the following days levels reach near normal (122) (V). In the study by the author, levels of F1+2 were greatly increased at admission, but decreased towards normal on the following days (VI).

The FM test performed on plasma from the same patients showed very high levels at admission. The levels declined during the following days, but they did not become normal during the first week after admission (V). Another study showed highly raised levels of TAT immediately after severe trauma (20 min) (124) and at admission to the emergency unit. In the study by the author, TAT levels were also higher on admission, declining on the following days but remaining considerably above normal in the first 7 days after trauma (VI).

The urinary excretion of FpA in trauma patients is about 50-fold higher than in healthy controls with normal plasma levels of FpA (IV). This observation may suggest that FpA generation was highly increased in spite of only marginally raised plasma levels in the posttraumatic period. The posttraumatic plasma fluctuation in levels of F1+2 seems to be similar to that of FpA; likewise, F1+2 immunoreactivity is detected in the urine from trauma patients. The urinary immunoreactivity of F1+2 was higher than the corresponding plasma levels, and the excretion was almost 100 times that of healthy controls. On the other hand, TAT immunoreactivity was virtually not detected in the urine from the trauma patients, which may suggest that the larger TAT molecule is not excreted in the urine. It is possible that the urinary levels of FpA and F1+2 are more sensitive indicators of the coagulation turnover than measurement of the plasma levels of these peptides.

The observations on urinary FpA and F1+2 in trauma patients are at present preliminary and need further investigation. Alterations in renal excretion and handling may occur in the posttraumatic period, and the antigenic properties of the molecules may change in the urine (IV).

Assays for D-dimers, FbDP, TDP, or FgDP, which use monoclonal antibodies, have been used to detect haemostatic activation in plasma samples from trauma patients. Lampl et al measured these 4 markers in samples taken from trauma victims within the first 30 min after the incident (125). All the markers were about 20 to 50 times above normal levels. The next sample was taken within 58 to 98 min after the incident, at which time levels of FgDP and fibrinogen were significantly decreased. The other markers, virtually reflecting fibrin derived degradation products, did not change between the two samples (125). Plasma and serum levels of FDP decrease to near normal from day 1 to day 3 after trauma, but a second rise in levels of FDP has been observed by the author and other investigators at the end of the first week after trauma (122,126) (V). These findings were not confirmed in another study (123). However, comparisons are difficult, since the most traumatized patients in the last named study were given gabexate mesilate (a protease inhibitor with high affinity for thrombin).

This secondary increase in plasma levels of FbDP, occurring between the 3th and 7th day after surgery and trauma (II,V), may reflect wound healing associated fibrin degradation and dissolution of other extravascular or intravascular fibrin clots. But it may also be a response that opposes the possible secondary increased fibrin production in the postoperative/traumatic period (see 3.4).

High levels of t-PA:ag and t-PA activity were observed immediately after severe trauma, but within the next 11/2 h a 10-fold fall occurred for both measures of t-PA. PAI activity levels rose significantly during the same period (125). PAI activity levels were measured in serially taken blood samples from trauma patients who were admitted within 1 h after the incident (127). The normal admission levels of PAI activity rose to peak levels 12 h after admission. A steady fall towards normal PAI activity levels then occurred within 24 h after trauma. No further increase was seen within the first 4 posttraumatic days. Levels of t-PA:ag, PAI-1:ag, and PAI-1 activity were increased in 19 patients with multiple trauma, and levels of α-2-antiplasmin were low at admission (11/2 to 7 h after trauma) (VII).

Levels of t-PA:ag normalized during the first week, whereas PAI-1:ag levels decreased gradually from day 1 to day 3, after which a secondary increase was observed. A similar trend occurred in levels of PAI activity. Levels of α-2-antiplasmin increased to above normal levels (VII). The general assumption is that the fall in plasma profibrinolytic activity (decreased t-PA activity/increased PAI activity) is due to increased liberation of PAI, which subsequently inactivates free t-PA, leading to decreased or impaired
fibrinolysis. On the other hand, fibrin degradation is accomplished when the active t-PA molecule is adsorbed on the fibrin surface activating the adsorbed plasminogen (49). The postoperative-traumatic fall in t-PA activity could therefore be an indication of increased t-PA adsorption on fibrin. This would result in increased rather than decreased fibrinolysis. The concept that low plasma levels of t-PA activity are an indication of reduced fibrinolysis after surgery and trauma may then be challenged (VII).

3.8 Haemostatic tests after traumatic shock
Traumatic haemorrhagic shock may be defined as a significant loss of blood volume due to trauma, which during resuscitation necessitates multiple blood transfusions in order to maintain adequate tissue perfusion. Clinical studies concerning the influence of traumatic haemorrhagic shock on coagulation tests are sparse. However, the influence of massive transfusions on conventional coagulation tests has been studied in trauma patients. Prolongation of partial thromboplastin time, prothrombin time, and APTT has been observed shortly after multiple transfusions, but 15 h later the values were near normal. After day 2 the test results were normal. Levels of fibrinogen, factor V, and factor VIII are initially low, but they increase during the post-traumatic period; raised values have been seen on day 2 (128,129). Raised levels of serum FDP were observed in a majority of patients during an observation period of 25 days after haemorrhagic shock (129).

3.9 Haemostatic activation after burn injury
Severe burn injury is also associated with considerable alterations in haemostatic tests, and the response pattern is similar to that in trauma patients (130,131).

3.10 Discussion
Brain, lung, and epithelium of the skin possess large amounts of tissue factor (132). Most authors find it plausible that tissue thromboplastin released from the wound activates the extrinsic coagulation pathway, which stimulates fibrin formation. It has been suggested that the release of vasopressin from the posterior pituitary may mediate haemostatic activation during operations, since a close temporal relationship exists between the rise in plasma vasopressin levels and the rise in FpA levels during operation (72). Other neurophysiological mechanisms may contribute to the haemostatic activation during and after surgery and trauma, since the global coagulation time decreases during experimental haemorrhage (133) and levels of FpA increase in dogs after infusion of adrenaline (134). Nygaard et al demonstrated increased thromboplastin activity in systemic circulating blood monocytes after total hip replacement, and suggested that this might play a part in the induction of a postoperative prethrombotic state (135).

For the different markers of coagulation and fibrinolysis, several reservations must be considered when interpretations of the plasma levels are made.

1) Measurement of the haemostatic markers in plasma does not distinguish whether the plasma levels are the result of local activation, local release, or systemic haemostatic activation.

2) Differences in plasma half-life may exist between the different haemostatic markers, and the plasma half-life may change due to alterations in the metabolic and excretion behaviour.

3) A wide inter-individual range of the markers was observed in the investigated patients.

It is suggested from the author's studies (I-VII) that the immediate effect on the haemostatic system of hip replacement surgery, isolated fractures of the hip, femur, and leg, isolated head injury, and multiple trauma is activation of both fibrin formation and fibrin degradation pathways. This could be due to the release of procoagulant activity from the wound and the release of profibrinolytic activity, which may originate from the endothelium. A temporary fall towards lower levels of the coagulation markers occurs during the first postoperative and the posttraumatic days, but levels are above normal in the first week, suggesting continuing activation of coagulation. This may possibly reflect a secondary activation of the haemostatic system, promoted by the inflammatory processes in the wound healing sequence and procoagulant activity released when the haemostatic plugs are degraded. As indicated by increased levels of fibrin/fibrinogen degradation products, a secondary increase in fibrin degradation is observed between the 3rd and 7th day. This may reflect increased degradation of fibrin as a response to the increased fibrin formation in this period, degradation of fibrin in the wound, and degradation of intravascular fibrin.

The work by the author does not reject the hypothesis that the changes in the blood after surgery and trauma, as determined by the haemostatic markers, are a consequence of a dynamic haemostatic balance, and that this may be considered as a normal physiological response to tissue injury and repair.

4 Haemostatic activation and relationship to clinicopathological findings after surgery

4.1 Introduction
A variety of complications which occur after elective surgery and trauma have been attributed to the haemostatic system. They include cardiopulmonary impairment during hip surgery, postoperative traumatic deep vein thrombosis and pulmonary emboli, postrummatric pulmonary dysfunction, and posttraumatic disseminated intravascular coagulation. This chapter surveys the literature and presents the author's experience concerning the
relationship between complications after surgery and the haemostatic system.

4.2 The relationship between cardiopulmonary dysfunction during hip surgery and haemostatic activation

Cardiopulmonary changes during total hip replacement (THR) using cemented components include hypoxaemia, hypotension, cardiac arrest, and sudden death. The intraoperative mortality ranges from 0.02% to 6.6% (136). A transient fall in arterial partial oxygen saturation (PaO₂) occurs immediately after the insertion of the cemented femoral component (60,137). Several pathogenetic factors have been suggested (138). Orsini et al demonstrated that the pressurizing effect of bone cement on producing high intramedullary pressure caused pulmonary microemboli in dogs (138). The pulmonary microemboli contain fat, a variety of bone marrow cells, platelet aggregations, and small fibrin plugs, which are released from the intramedullary cavity during instrumentation and insertion of the femoral component (58,138,139). Infusion of bone cement (monomethylmethacrylate) into dogs did not affect clotting tests or produce pulmonary trapping of fibrin and platelets, and no change in pulmonary function was recorded (140). A marked increase in circulating FpA, F1+2, and TAT levels, and a reduction in plasma coagulation time, when recalcified, are observed at the time of instrumentation and insertion of the femoral component, suggesting that thromboplastic containing material is released (58,68-71). Patients undergoing THR were given 51Cr labelled platelets and 125I labelled fibrinogen the day before operation (141). A transient accumulation in the lungs of 51Cr radioactivity and 125I radioactivity was recorded during femoral bone manipulation and after impaction of the femoral component. When the tourniquet used for bloodless field during total knee replacement was deflated, transoesophageal echocardiography revealed showers of echogenic material crossing the right atrium and ventricle and the pulmonary artery (142). Conclusive evidence has not yet been established for a causal relationship between cardiopulmonary impairment and activation of the haemostatic system during hip surgery.

4.3 Haemostatic tests and relationship to post-operative venous thromboembolism

Patients who undergo major surgery are exposed to a risk of venous thromboembolism, which accounts for a significant part of the morbidity and mortality after surgery (143). The frequency of non-symptomatic postoperative thromboembolism depends on the diagnostic method used. A variety of methods have been used for the detection of non-symptomatic postoperative deep vein thrombosis (DVT); bilateral phlebography, I-125-fibrinogen scanning, impedance plethysmography, and doppler or real-time B-mode ultrasound. Very poor agreement between the different methods has been reported when they are used for screening of postoperative DVT (144-146). At present, bilateral phlebography is considered to be the reference standard for screening of non-symptomatic postoperative DVT. However, the interpretation of bilateral phlebograms obtained from postoperative patients seems to be highly dependent on the observer, since interobserver variation is pronounced (147). Many attempts have been made to relate different coagulation and fibrinolytic tests to the occurrence of postoperative venous thromboembolism, but conflicting results have often been reported.

4.3.1 Studies in general surgery

Several studies on patients undergoing elective abdominal, urological, and gynaecological surgery for benign or malignant diseases have observed lower preoperative fibrinolytic activity, as measured by global fibrinolytic tests, in patients in whom postoperative DVT developed (90,94,148-151). Other authors have not found differences in preoperative global fibrinolytic tests between patients with and without postoperative DVT (63,95-97,152-155). Aranda et al reported that preoperative PAI activity levels were significantly higher in patients in whom DVT developed, but levels of t-PA activity and t-PA antigen were not different (94). Other studies measured the preoperative t-PA inhibition activity, but no differences were seen between patients with or without DVT (98,151,156). Likewise, no significant differences in preoperative levels of t-PA activity and antigen levels have been observed between patients with and without postoperative DVT (151,156). Significantly lower preoperative levels of plasmin-α-2-antiplasmin complex have been reported in patients who developed postoperative DVT (157). The findings of preoperative differences in the fibrinolytic tests cannot be interpreted as proof of a causal relationship between impaired preoperative fibrinolytic activity and the development of postoperative DVT. Clearly, other significant differences existed between the patients who developed DVT and those who did not. DVT patients are older (148,150,151) and their operations are more often for malignant diseases, which may require more extensive surgery (148,150,158). The possibility that the preoperative fibrinolytic tests were confounded by high age and malignancy has been given very little attention. The above-mentioned assays have also been performed on postoperative plasma samples. In a study on 28 patients, the fibrinolytic activity, determined by a 125-I-fibrin digestion technique, was higher 48 h after the operation in the 9 patients who developed postoperative DVT (97). As determined by the dilute blood clot lysis test and the fibrin plate lysis area, patients with postoperative DVT had a higher reduction of fibrinolytic activity on the first postoperative day (95). The fibrinolytic activity, as determined by a timed fibrin digestion technique,
revealed that the DVT patients had significantly lower fibrinolytic activity on the first postoperative day. However, on the following postoperative days, no differences in fibrinolytic activity existed between the patients (96). Similar observations were made by others, who found that the dilute blood clot lysis time and the ECLT were significantly longer on the 1st postoperative day in DVT patients (90,154). Other studies found no differences in the ECLT or in fibrin plate activity when patients with and without DVT were compared (63,94,153). In a study on orthopaedic and urological patients, using whole blood dilute clot lysis assay, patients who had normal test results in pre- and postoperative samples had a 1% risk of postoperative DVT, whereas the incidence of DVT was 28% in patients who had one abnormal assay, and 56% in patients with three abnormal assays (159). In another study t-PA activity and antigen levels were not different in the postoperative period when patients with and without DVT were compared (94). Individual increases in t-PA inhibition from pre- to postoperative days were significantly higher in patients with DVT (98). It has also been reported that t-PA antigen levels decreased from preoperative to postoperative in patients who developed DVT, whereas patients without DVT showed an increase in t-PA antigen levels from preoperative to postoperative (160). In a study comprising 36 patients, postoperative levels of serum FDP were significantly higher in patients who had either DVT or PE than in patients without thromboembolism (161). This finding was not confirmed in another study (153).

A study on patients who underwent major gastrointestinal surgery for malignant or benign diseases measured levels of FpA and fibrinogen fragment B\(\beta15-42\) in pre- and postoperative samples (80). 14 of the 32 patients developed postoperative DVT. The DVT patients had higher levels of FpA on the 7th postoperative day and higher B\(\beta15-42\) on the first postoperative day than the patients without DVT.

### 4.3.2 Studies in elective hip surgery

The relationship between haemostatic tests and the development of non-symptomatic thromboembolism after THR has been investigated during the past 10 years. In contrast to the studies on general surgery patients, the group of elective hip surgery patients is more uniform with respect to the preoperative disease status, undergoing a standard operation (trauma) and following a standard rehabilitation programme. The use of elective hip surgery patients may partly overcome the difficulties and considerations concerning possible confounding linkages between concurrent disease, age, type of operation, and the haemostatic tests.

In five studies, the observation was made that preoperative PAI-1 activity levels were significantly higher in patients in whom postoperative non-symptomatic thromboembolism developed than in patients without (101,102,162-164). In another study no such difference was observed (165). However, significantly lower preoperative levels of t-PA activity have been found in patients with postoperative DVT (103). Levels of PAI activity, PAI antigen, and t-PA antigen were higher 15 min after surgery and on day 1 in patients who later developed thromboembolism (102). PAI activity and t-PA antigen levels on day 7 were also higher in patients with thromboembolism (101,102). However, the other studies did not find these differences in the postoperative period (103,162,164,165).

This survey suggests that low plasma profibrinolytic activity is associated with the development of postoperative thromboembolism. A causal relationship has not been demonstrated, and it remains to be established whether a preoperative or a postoperative modulation of the plasma profibrinolytic activity may influence the occurrence of postoperative thromboembolism after THR. Postoperative levels of FDP seem to be significantly higher in patients with DVT (87,106). In the study by the author in patients who had no pharmacological thromboprophylactic medication, levels of TDP were significantly higher on day 7 in patients who had DVT. But due to a wide overlap between groups with and without DVT, levels of TDP were without predictive power for the identification of patients with DVT. In patients who had low molecular weight heparin (LMW-heparin) for prophylaxis, no significant difference was observed between groups with and without DVT (II). FpA levels did not differ between patients with and without DVT in a rather small study (85). In the author's study, the F1+2 levels postoperatively were significantly higher in patients with DVT, who received no anticoagulants, than in patients without DVT, who received no anticoagulants (II). Levels of F1+2 were without predictive power for DVT. In the group who had LMW-heparin for prophylaxis, no differences in levels of F1+2 were observed between patients with and without DVT. Postoperative levels of TAT have also been observed to be higher in patients with DVT (86,87,106). A trend towards such differences was seen in the study by the author, but it was not statistically significant (I). The prophylactic use of low molecular weight heparin (LMW-heparin) reduces the incidence of non-symptomatic DVT after elective hip surgery (166). The mechanisms by which this is accomplished are not yet fully understood. In studies by the author and others, no influence of prophylactic dosages of LMW-heparin on levels of t-PA and PAI has been observed (102,103,165). In the study by the author (I), postoperative levels of TAT did not differ significantly between patients who had LMW-heparin and patients who had placebo (I). On the other hand, in the larger study (II), levels of F1+2 were significantly lower in patients who had LMW-heparin, and day 7 levels of TDP were significantly lower in the LMW-heparin group (II). The results may support the hypothesis...
that the prophylactic administration of LMW-heparin reduces thrombin turnover, which possibly reduces the amount of fibrin available for plasmin degradation in the postoperative period. A further discussion of suggested and postulated mechanisms is beyond the scope of this presentation.

4.4 Conclusions

No haemostatic test has so far provided a satisfactory predictive power for the discrimination between patients with and without non-symptomatic postoperative DVT. The following factors presumably contribute to the conflicting findings concerning the relationship between postoperative DVT and haemostatic tests: differences in the haemostatic tests used, heterogeneous patient groups, patients undergoing different types of operation, patients receiving different kinds of thromboprophylaxis, and, as mentioned, differences in and difficulties with the diagnostic methods used for the detection of non-symptomatic thromboembolism.

It is possible that thrombotic events may not be restricted to the deep veins of the lower extremities (see 6.4). The clinical significance of the detection by phlebography of non-symptomatic DVT on a particular day in the postoperative period seems to be unclear. To elucidate a possible clinical usefulness of the haemostatic markers, it is suggested that studies should be performed concerning the relationship between haemostatic markers and clinical events, such as symptomatic postoperative cardiopulmonary disease and postoperative mortality. However, lack of methods for proper quantitation of cardiopulmonary symptoms may complicate such studies.

5 Haemostatic activation and relationship to clinicopathological findings after trauma

5.1 Introduction

The capacity to increase fibrin formation after trauma may, as previously mentioned, be an important factor in wound haemostasis. However, several observations suggest that fibrin formation after trauma is not restricted to the wound only. Experimental studies, autopsy studies, and paraclinical studies suggest that intravascular fibrin deposition is common after haemorrhage and trauma. This chapter presents such studies, and studies on the relationship between haemostatic tests and clinicopathological findings in patients after trauma.

5.2 Experimental studies, autopsy studies, paraclinical studies

Turpini and Stefanini observed intravascular deposition of fibrin and platelets in the lung, kidney, and liver in rabbits after severe haemorrhage, though not in previously splenectomized animals (167). These observations, which suggest that the spleen is an important mediator of haemostatic activation after haemorrhage, were reported several decades earlier by McClintock and Magers, who noted shortening of the clotting time in dogs after haemorrhage, but not when the dogs were splenectomized (168). Their study was based on the classical study by Gray and Lunt, who found that exclusion of the abdominal circulation increased clotting time, and that severe haemorrhage did not decrease clotting time when the abdominal circulation was excluded (5). The experimental studies on haemorrhagic shock were later continued by Hardaway in 1963. In the first study (169), 28 dogs were subjected to haemorrhagic shock for $2^{1/2}$ h, after which the blood was retransfused. 14 of the dogs were additionally given streptokinase, the rest acting as controls. 11 dogs in the streptokinase group survived, whereas only 3 survived in the control group. In the second study (170), dogs were divided into 3 groups. 15 dogs were controls as in the first study. Another 15 were treated with streptokinase. The third group of 9 dogs was not bled, but received streptokinase. Within 24 h, 11 control dogs died, while 4 in the treated group died. All the dogs survived which received streptokinase only. In experimental closed minor head injury in rats, pretreated with epsilonaminocaproic acid (EACA), which inhibits plasminogen binding to fibrin, fibrin deposition in the pulmonary vessels was seen shortly after the injury. These changes were not seen in animals which underwent the same treatment, except for the head injury (171).

Using radiolabelled platelets and fibrinogen for external detection of pulmonary deposition of radioactivity, pulmonary microembolism was observed after musculoskeletal trauma of a hind limb in pigs (172). In another study, anaesthetized pigs were subjected to major soft tissue injury of the outer thigh (173). 9 untreated dogs died within 48 h, whereas 5 animals treated with streptokinase and 5 animals treated with tissue plasminogen activator survived, treatment having started 4 h after trauma (173). The relative importance of the lung fibrinolytic capacity was demonstrated by Saldeen, who injected thrombin intravenously into rats (174). After 5 to 10 min fibrin deposits were found regularly in small lung vessels, but less often after 15 to 30 min, and only in a few isolated vessels after 60 min. When rats were pretreated with EACA, the fibrin deposits were not eliminated from the lungs. The injection of human tissue thromboplastin into rats gave virtually the same response as seen for thrombin (175). After injection, the rats developed marked dyspnoea, which lasted from 5 to 15 min. When the dosage was increased, the animals died in respiratory distress. Defibrinogenation of animals prior to treatment with thrombin and tranexamic acid (AMCA), which inhibit plasminogen binding to fibrin, prevented...
pulmonary insufficiency, whereas isolated leucopenia or thrombocytopenia did not (176).

In the classical study by Sevitt and Gallagher on the prevention of pulmonary embolism in patients with hip fracture, autopsy studies were performed in patients who died during the study period (177). The incidence of lethal pulmonary emboli was 2% in patients who were given phenindione, while it was 14% in the control group. In the autopsy study on burned and injured patients by the same authors, deep vein thrombosis was demonstrated in 65% and pulmonary embolism in 16% (178). Later, Eeles and Sevitt found that lung microthrombosis was a frequent pathological finding in patients who died from trauma (179). Pulmonary microthrombosis was most often seen in patients who died within 3 h after trauma and in patients in whom injury and haemorrhage were severe. Microthrombi were less frequent in patients who died 2 or more days after injury, but in some cases, when microthrombi appeared, signs of organization were seen. Pulmonary arterial microthrombi and macrothrombi were found in 20% of patients who survived for more than a week (179). Lindquist et al performed autopsy studies on 28 patients who had sustained severe trauma, excluding patients with head injury and patients who died within 24 hours after trauma (180). They found pulmonary fibrin deposition in all the patients, and in 20 this was considered to be responsible for the fatal outcome. In the autopsy study by Kaufman et al on patients with severe head injury who died within the first 2 days after admission, microthrombi were frequently found in the brain, liver, and lungs (181). Blaisdell et al, in their autopsy study on patients who died after major vascular surgery, found that pulmonary microembolism was a common causative factor in postoperative mortality and morbidity (182). Trapping of radiolabelled fibrinogen in the lungs, determined by external detection of radioactivity, was demonstrated in patients who developed pulmonary insufficiency after trauma (183,184).

The incidence of posttraumatic deep vein thrombosis, as determined by phlebography, is reported to range from 18% to 90%, with the highest risk in elderly patients and in patients with spinal injury (185). The risk of pulmonary embolism ranged from 4% to 22% (185). In a one-year retrospective review of 1316 patients who were admitted to a trauma centre, 30 cases of symptomatic pulmonary emboli, diagnosed by pulmonary angiography, were found, and 7 died from this complication (186).

The experimental animal studies, the autopsy studies, and the clinical studies using paraclinical methods suggest that intravascular fibrin deposition in the form of macrothromboemboli or microthromboemboli is common after trauma, and the possibility that intravascular fibrin deposition may play a pathogenetic role in the development of posttraumatic organ dysfunction is likely. Consequently, an attractive approach would be to search for haemostatic tests which could identify patients in whom posttraumatic organ dysfunction would develop, and predict a fatal outcome.

5.3 Relationship between injury severity and haemostatic tests

Haemostatic abnormalities, as determined by conventional coagulation tests, are reported to be more pronounced in patients with severe head injury than in patients with less severe head injury, as quantified by the Glasgow Coma Score (GCS) or Cranial computer tomography scans (120,187,188). Virtually no statistical differences were observed in the posttraumatic levels of F1+2, TAT, FpA, FM, and FbDP when patients with isolated head injury were compared with patients with multiple trauma, although the latter group showed a trend towards higher levels of all markers, and levels of TAT were significantly higher in the multiple trauma group (V, VI). Weak, but significant correlations were seen between admission levels of F1+2, TAT, FpA and the anatomically based Injury Severity Score (ISS) (189), whereas admission levels of fibrinogen were inversely correlated to the ISS. A correlation between the markers and the coma score, assessed by the GCS (190), was not detected, but this may be due to too few observations since only 14 patients had isolated head injury. In other studies, levels of D-dimer in the posttraumatic period were correlated to the ISS (126,191).

In study VII, the plasma profibrinolytic and antifibrinolytic factors, t-PA:ag, PAI-1:ag or PAI-1 activity, were not correlated to the ISS on any day, but levels of α-2-antiplasmin showed a weak correlation to the ISS on day 7.

Levels of F1+2, TAT, FpA, FM, and FbDP were not significantly different in patients who received or did not receive blood transfusions (V,VI). On the other hand, posttraumatic levels of tPA:ag and PAI-1:ag were higher in patients who had 6 or more units of blood transfused during resuscitation (VII). Whether the observed differences are a consequence of haemorrhage or of multiple blood transfusions is present not clear (VII).

5.4 Relationship between haemostatic tests and posttraumatic mortality and disseminated intravascular coagulation

Attar et al, in 1969, performed serial haemostatic analyses on 54 trauma patients during the initial hours after admission (192). In 15 patients who died, the silicone clotting time, prothrombin time, and partial thromboplastin time were significantly prolonged, compared with values in the surviving group. Levels of fibrinogen, platelets, VIII, IX, X, and plasminogen were significantly lower in the fatal cases. Thrombin time, antithrombin titre, plasminogen activator activity, and plasmin activity did not differ between survivors and fatal cases. The incidence of shock (arterial blood pressure below 90 mmHg) did not influence the haemostatic tests. No information was given concerning trauma score
or death from posttraumatic organ failure. Similar differences between survivors and nonsurvivors, using similar haemostatic tests, were observed in 18 American servicemen wounded in the Vietnam war (193). In a study on 15 trauma patients using serial chromogenic peptide substrate assays, plasma levels of prekallikrein, plasma Hageman factor, ATIII, and prothrombin were significantly lower in 6 patients who died from sepsis and/or posttraumatic adult respiratory distress syndrome (ARDS) (194); the fatal cases had raised serum FDP, whereas levels were within normal range in the survivors (195). Risberg et al studied 20 patients with multiple trauma, of whom 5 developed DIC (122). DIC was diagnosed by raised serum FDP, reduced platelet count, and a positive ethanol gelation test, in addition to the presence of clinical signs of diffuse bleeding or organ failure. 3 DIC patients died from multiple organ failure, and 4 non-DIC patients died, 3 from brain injury and one from pulmonary embolism. Early studies on patients with head injury suggested that the occurrence of DIC was a common phenomenon associated with a high mortality rate (116,196-198). Sande et al performed coagulation studies on 150 patients who were admitted after blunt head injury, of whom 10 died (114). Serum FDP levels were 80 µg/ml or more in 13 patients, eight of whom died. Miner et al studied 87 children with head injury, of whom 22 died (199). DIC was defined as the presence of 3 or more abnormal clotting tests among the prothrombin time, APTT, platelet counts, fibrinogen level, and serum FDP in samples taken within 2 h after admission. According to these criteria, 32% had DIC, and in these the mortality was 54%, compared with 12% in the patients without DIC. Even after correction for the severity of the injury, a clear relationship between 3 abnormal coagulation tests and mortality existed. Kumura et al used a similar definition of DIC in their study on 100 patients with head injury (200). 24 had DIC by these criteria, of whom 14 died, whereas only 5 of 76 patients without DIC died. A multivariate analysis showed that the levels of the APTT assay and the GCS were most closely correlated with the prognosis. Olson et al, in a study of 269 patients with isolated head injuries, registered admission GCS, platelet counts, prothrombin time, APTT, thrombin clotting assay, fibrinogen, serum FDP, and a DIC score based on these assays (187). No specific information was given concerning the cause of death of 96 patients. A stepwise logistic regression analysis demonstrated that the GCS, serum FDP levels, and DIC score had predictive value for mortality.

5.5 Relationship between haemostatic tests and the development of posttraumatic pulmonary dysfunction

Impairment of pulmonary function in patients who suffer trauma remote from the lungs has been known for many years, and the syndrome has been given many names, including fat emboli syndrome, white lung syndrome, shock lung syndrome, traumatic wet lung, and pulmonary microembolism. The term Respiratory Distress Syndrome in Adults (ARDS) was introduced by Ashbaugh et al (201), who noted that the postmortem findings in trauma patients who died from respiratory failure were similar to those seen in infants who died from respiratory distress. The term ARDS was later widely adopted, but various clinical definitions have been used. The incidence of posttraumatic pulmonary dysfunction (PD) is between 6% and 20%, depending on the type of trauma and the definition used (172,202-204). In studies on patients with fractures of the lower limbs, it was noted that many patients had abnormally low levels of PaO₂, which was interpreted as subclinical fat embolism (112,113). A connection between the fat embolism syndrome and the coagulation system was suggested, but this could not be established by measurement of platelets and fibrinogen. In the study by the author on patients with fractures of the lower extremities, the posttraumatic lung function was not quantified (III). Cardiopulmonary symptoms are very common after hip fracture in older patients, and the symptoms are often interpreted as pneumonia, myocardial infarction, or congestive heart failure. In the study by String et al, 40 patients with multiple trauma were divided into three groups according to the degree of posttraumatic PD (205). The first group consisted of 13 patients who needed ventilatory support for more than 3 days, and who had bilateral diffuse reticular infiltrates on chest X-ray. Many of these patients developed multiple organ failure. The second group consisted of 16 patients who developed only moderate degrees of PD, and respiratory support was limited to less than 3 days. The third group consisted of 11 patients with little or no evidence of PD. Coagulation changes were most severe in the first group, with low levels of coagulation factors I, II, V, VII, VIII, and IX, low thrombocyte counts, and high levels of FDP. Coagulation changes were less severe in the second and third groups. In that study, however, it was not stated when the blood samples were taken, and the severity of injuries was not quantified. Crone et al studied 33 patients with severe closed head injury with GCS less than 8 (206). Nine of 11 patients who had admission levels of serum FDP > 6 µg/ml developed ARDS during the first 2 days, compared with only 1 of 22 patients with serum FDP < 64 µg/ml. Schramm et al studied 52 polytrauma patients, of whom 24 developed ARDS (no definition was given) (207). PAI activity levels were significantly higher in patients with than without ARDS. The AT III levels were significantly lower in the ARDS group at 6 h, 12 h, and 24 h after the trauma. Levels of D-dimers were reported to be higher in the ARDS group, but this was not statistically significant. In another study the authors suggested that a secondary elevation of D-dimer levels was indicative of pathological
thrombosis since a patient with pulmonary embolism, another with ARDS, and a third with sepsis syndrome had highly raised levels 7 days after trauma, whereas patients without these complications had less raised levels (126).

Seeger et al studied 25 multiple trauma patients by serial determinations of recalcification time (RT) in the presence or absence of phosphatidylserine. In bronchoalveolar lavage (BAL) fluid (208). 11 patients had a high ARDS score, and 14 a low score. With respect to age and ISS no significant difference existed between the 2 groups. The RT was lower in the patients than in healthy controls. Patients with a high ARDS score had significantly lower RT from day 4 to day 12 after trauma than patients with a low ARDS score. However, no such difference was seen during the initial 3 posttraumatic days. In another study on 8 patients with established ARDS (2 cases due to trauma), BAL fluid contained decreased urokinase activity, presumably due to inhibition by PAI-1, since urokinase antigen level was normal (209). In a similar study, plasminogen activator inhibitor activity in the BAL fluid was depressed in 14 ARDS patients (6 cases due to trauma) and plasmin mediated fibrinolysis was low, but levels of plasminogen and α-2-antiplasmin were higher in the ARDS group (210). Both extrinsic pathway inhibitor activity and tissue factor procoagulant activity were higher in patients with ARDS compared with patients at risk of ARDS. In both these last named studies it was concluded that increased antifibrinolytic activity predisposed to alveolar fibrin deposition in ARDS. However, in these studies it is difficult to tell whether the reduced fibrinolytic capacity of BAL fluid had a pathophysiological role in the development of ARDS or was simply a consequence of ARDS.

In the study by the author, admission plasma levels of F1+2, TAT, FpA, FM, or FbDP were highly raised, but no differences were observed in patients who later had PD compared with patients without PD (V,VI). Consumption and loss of coagulation zymogens during the initial minutes after trauma may have been more pronounced in the patients who later had PD, resulting in lower levels of coagulation zymogens. Therefore the possibility remains that a more marked activation of coagulation and fibrinolysis was overlooked in the patients with PD, since blood sampling in many cases was delayed 3–4 h after the trauma.

Four patients who developed PD had significantly lower levels of F1+2 and FbDP on the day after admission than patients without PD. On the following days no difference was observed in levels of the markers when patients with and without PD were compared. Due to the low number of patients with PD, the statistical evaluation must be considered with reservation. However, the observations may suggest lower thrombin and plasmin activity in the patients with PD on the day after admission. On the other hand, since levels of TAT, FpA, and FM were not lower in patients with PD, the finding of lower F1+2 levels in these patients seems unclear. The trend towards lower FbDP levels in patients with PD seems to be in accordance with previous observations, which suggest that the pulmonary fibrinolytic capacity is critical in the prevention of pulmonary fibrin deposition. On the other hand, consumption and loss of coagulation zymogens may have been more marked in these patients, resulting in a lower generation rate of F1+2 and FbDP.

Further investigations concerning plasma levels of t-PA and PAI-1 and α-2-antiplasmin were performed on 19 patients who had sustained multiple trauma and of whom 4 developed PD. Levels of PAI-1 antigen, PAI-1 activity, t-PA antigen, and α-2-antiplasmin did not differ between patients with or without PD.

The definition used for PD was based on an arbitrarily chosen level of a functional index for the respiratory function, which was used in a similar study (206). It is the author's experience that the majority of trauma patients had considerable impairment of the respiratory function especially on day 1, as determined by the functional respiratory index; however, only 4 patients fulfilled the chosen criteria for PD.

5.6 Conclusions
Plasma levels of the different markers of coagulation and fibrinolysis seem to be correlated to some extent to the severity of the injury.

The author's findings do not reject the hypothesis that the haemostatic system plays an important pathophysiological role in the development of PD after trauma. On the other hand, the haemostatic tests used in this study were unable to identify patients in whom PD developed. Any clinical relevance of these haemostatic tests in trauma patients has so far not been provided.

6 Perspectives of the haemostatic activation after tissue injury

6.1 Introduction
The hypothesis of the previous chapters was that part of the fibrin that is generated after injury may be deposited in the wound, facilitating haemostasis, that a second part may immediately be degraded, resulting in FDP, and that a third part may be deposited somewhere in the vascular system, for a longer or a shorter period, as micro- or macrothromboemboli, causing more or less obstruction of blood flow.

This chapter includes a presentation of the possible physiological reactions of fibrin/FDP located in the wound and possible pathophysiological reactions of fibrin/FDP in the vascular system. Based on these considerations, the author suggests a model for the interpretation of the possible linkages between
the haemostatic system, wound healing, organ dysfunction, and thromboembolism after surgery and trauma.

6.2 Fibrin and wound healing
Fibrin deposition in wounds may be interpreted as a major defence mechanism against exsanguination, and may provide a physical framework on which inflammation and angiogenesis can occur, leading to repair and healing. The antigenic properties of fibrin and fibrin degradation products seem to be important (1,211), as well as the composition and concentration of the fibrin gel, which are determinative factors for cellular infiltration (212,213). The haemostatic activation process after trauma may therefore be the initial step in a cascade of inflammatory reactions, which leads to healing of the wound. However, inflammatory cells, including fibroblasts and macrophages, may aggregate on fibrin matrices which are not situated in a wound (212,213).

6.3 Fibrin/FDP and initiation of increased permeability and inflammation
The possible relationship between fibrin microemboli/FDP and increased endothelial permeability has been the object of several studies. Experimental observations suggest that pulmonary oedema following pulmonary thromboembolization with glass beads is due to secondary fibrin formation and not mechanical obstruction, since animals pretreated with heparin did not develop pulmonary oedema (214). Increased pulmonary vascular permeability and increased leakage of protein in the pulmonary interstitial spaces were seen in dogs which were given thrombin and AMCA. Ultrastructural studies showed that the leakage occurred across the endothelial cells (215).

It was observed in other experimental studies that fibrinogen degradation product D, when injected intravenously into rabbits, produced progressive PD and interstitial pulmonary oedema (216,217). A permeability increasing pentapeptide and an undecapeptide derived from fibrin and fibrinogen have been isolated (218). Oedema in the alveolar and interstitial spaces in the lungs is a common autopsy finding in patients who die from trauma (172). Damage to the alveolarcapillary membrane and aggregation of polymorphonuclear leucocytes are early morphological findings in trauma patients (219). In patients who have suffered ARDS for more than four days, fibroblast proliferation and deposits of collagen are superimposed (172). The possible effects of fibrin are illustrated in Fig. 6.

6.4 Haemostatic activation, wound healing, organ dysfunction, and thromboembolism after surgery and trauma
Immediately after trauma, procoagulant activity from wounds, and possibly from the spleen, may be released directly into the venous circulation, promoting fibrin formation. It may be anticipated that most of the fibrin aggregates that are formed in the venous circulation will be trapped in the pulmonary microvascular system. When the blood then enters the arterial system it circulates for only a few seconds before it reaches a peripheral microvascular system, in which possible fibrin aggregates, formed during the passage from the lungs, are entrapped and lysed by the fibrinolytic system. On the other hand, when the blood returns to the venous system, the blood flow velocity is considerably lower than in the arterial system, about 5 cm/s (220). Relatively more fibrin may be generated during the blood passage from the peripheral veins to the pulmonary microvascular system than during the passage from the pulmonary circulation to the peripheral microvascular system. The lungs may thereby act as the organ of major importance in the clearance of intravascularly formed fibrin. Depending on the capacity of the fibrinolytic system in the lungs, the fibrin aggregates are quickly dissolved. If they are not quickly dissolved, the sequence of acute inflammatory reactions may ensue. These reactions may be a consequence of fibrin/FDP damage to the endothelial cells or of local activation and degradation of polymorphonuclear leucocytes, macrophages, and platelets, including liberation of histamine, bradykinin, serotonin, and prostaglandins. This may result in increased capillary permeability with subsequent exudation and congestion of the pulmonary parenchyma. These changes may later be followed by reparative proliferation by leucocytes and fibroblasts, resembling the processes of wound healing. These processes may be reversible for a period, but if they last long enough they may become irreversible, leading to fibrosis and organ damage. These pathophysiological reactions may progress to involve other organs such as the kidneys, gastrointestinal tract, heart, and brain.

The initial or early signs of PD after trauma may reflect both mechanical obstruction and acute pulmonary oedema due to the presence of fibrin and platelet plugs, whereas the later signs of organ dysfunction would be a consequence of progressive cellular inflammatory reactions. The fibrin, which primarily initiated the process, may be dissolved during the inflammatory steps. On the other hand, the inflammatory process may stimulate secondary coagulation activation, with fibrin formation and deposition. The initial hyperactivation of fibrin formation may be followed in the postoperative/traumatic period by a period of lowgrade increased fibrin formation, which may be a secondary phenomenon of the wound healing processes. Possible fibrin aggregates, formed in the leg veins and systemic veins in the postoperative/traumatic period, may not adhere to the vein wall, but may be transferred directly to the pulmonary circulation as pulmonary microemboli or fibrin aggregates, where they may be cleared by the pulmonary fibrinolytic system. However, in individuals with a low potential to resist fibrin
deposition in the lungs, the continuing increased stimulation of fibrin formation may overwhelm the local capacity to degrade fibrin, leading to the pathophysiological reactions of acute inflammation. Fibrin aggregates may also be able to adhere to the vein wall, if the local defence mechanisms are unable to oppose fibrin and platelet deposition, and propagation to larger vein thrombi may then take place. The vein thrombus may break up into larger or smaller fragments giving rise to pulmonary emboli, or it may remain attached to the vein wall undergoing lysis or organization and superimposed inflammation, which may lead to vein fibrosis. As a consequence of impaired venous drainage of the extremity, the postthrombotic syndrome may later develop.

Indeed, many pathogenetic mechanisms have been incriminated in the pathophysiology in ARDS and multiple organ failure (221-224). The suggested mechanisms include mediators of inflammation such as complement activation, neutrophil proteases, cyclooxygenase pathway products, oxygen radicals, lipoxygenase pathway products, and cytokines. After trauma and surgery, many patients suffer from cardiopulmonary symptoms, which are often considered to be pneumonia, myocardial infarction, or congestive heart failure. For the clinician it may be a very common experience that these patients do not improve when treated with antibiotics or diuretics. In many cases the symptoms disappear during the postoperative period, but in others the cardiopulmonary function continues to deteriorate, and they remain unresponsive to treatment. Havig, studying a mixed population of hospital autopsies, noted that, in 70% of patients who died from a pulmonary embolus or multiple pulmonary emboli, the preceding symptoms were undramatically dominated by dyspnoea, tachycardia, cerebral symptoms, and often fever (225). The symptoms were incorrectly attributed to cardiac disease, pneumonia or cerebrovascular disease in 90% of these patients. These symptoms often occur in patients with a fractured hip in the posttraumatic/operative period. These patients are often older, and they often suffer from cardiopulmonary disease with only a marginal cardiopulmonary reserve capacity. Consequently, even a minor reduction of the pulmonary capacity would lead to a catastrophic impairment of oxygenation.

In conclusion, the author finds it possible that the haemostatic activation followed by fibrin deposition in wounds should be considered as a major defence mechanism against bleeding after trauma. Furthermore, the author finds it possible that fibrin deposition in the wound initiates the wound healing processes by activation of the inflammatory reactions, which take over in the process of repair, proliferation, and angiogenesis in the wound. Deleterious effects may occur if the haemostatic activation becomes unbalanced, resulting in either an increased bleeding
tendency or intravascular fibrin deposition such as micro- or macrothromboemboli. Intravascularly situated fibrin may as a direct consequence impair blood circulation or damage the endothelium and initiate the acute inflammatory cascade reactions, leading to accumulation of interstitial fluid with subsequent congestion and oedema of the involved organ. It is suggested that the majority of the intravascularly formed fibrin is normally cleared in the pulmonary microcirculation by the fibrinolytic system. If the fibrin aggregates trapped in the lungs are not dissolved shortly after their appearance, the sequence of acute inflammation and interstitial fluid accumulation may supervene. Later, the processes of cellular proliferation and tissue repair may take place. The organ in which the intravascular fibrin clots are situated is mistaken for a wound by the inflammatory systems.

6.5 Possible future implications
The treatment of trauma patients has improved during the past 20 years. The initial resuscitation with ventilatory support and stabilization of the circulation in order to obtain adequate tissue perfusion and avoid prolonged periods of hypoxaemia are considered to be of major importance (226). Early stabilization of fractures of the lower extremities in multiple trauma patients may reduce the risk of pulmonary and other complications in the posttraumatic period (227). Much attention has been given to the occurrence of non-symptomatic DVT after operations. Particularly in the past 15 years, an immense number of studies have been performed in order to prove that the incidence of non-symptomatic deep vein thrombosis can be reduced by anticoagulant drugs, and that some of these drugs are better and safer than others. The object of clinical trials should be improved care of the patients. In order to obtain this when testing a new treatment, variables such as morbidity and mortality should be the end point in clinical trials. The triggering mechanisms for PD after sepsis, pancreatitis, aspiration, and cancer may not be the same as for the development of PD after trauma. This may have to be considered when treatment or prophylaxis is directed against supposed causative factors. Trials for the investigation of potentially beneficial drugs should therefore include only welldefined patient groups with the same underlying disorder. Otherwise any potentially beneficial effect of the treatment under investigation could easily disappear.

The suggested interactions between the haemostatic system and the system of inflammation and repair, which on one side lead to beneficial reactions and on the other side may lead to deleterious organ dysfunction, give, at least theoretically, several options for interventions. Anticoagulants may moderate fibrin formation, and administration of fibrinolytic drugs may increase the capacity to dissolve fibrin. Pharmacological treatment by corticosteroids, prostaglandins, and N-acetylcysteine may moderate the acute inflammation processes. Common to these drugs, when they are administrated to trauma patients, is that the potentially adverse effects may surpass the potentially beneficial effects. It is hoped that future studies will be able to elucidate whether trauma patients may benefit from treatment or prophylaxis by one or more of these drug categories.

7 Summary
The recent development of immunochemical methods has made it possible to construct assays which can quantitate the activities of various steps of the haemostatic system by measurements of split products and enzyme inhibitor complexes. It has been suggested that these methods may provide more sensitive and accurate information about the existing coagulation and fibrinolytic status than conventional haemostatic tests. The present study is an attempt to describe the influence of surgery, fractures of the extremities, neurotrauma, and multiple trauma on the generation of specific molecular markers of coagulation and fibrinolysis by newly developed immunochemical assays. Furthermore, it attempts to evaluate possible relationships between clinicopathological findings after surgery and trauma and haemostatic activation. The development and principles of the different coagulation and fibrinolytic assays are briefly reviewed. Values for normal individuals and the assay reproducibility are given.

The immediate effect of hip replacement surgery, isolated fractures of the hip, femur, and leg, isolated head injury, and multiple trauma on the haemostatic system is activation of both fibrinforming and fibrindegrading pathways, as measured by high levels of coagulation and fibrinolytic markers. This may be due to release of procoagulant activity from the wound and release of profibrinolytic activity, which may originate from the endothelium.

At admission, patients with fractures of the lower extremities showed relatively strong correlations between the different haemostatic markers, but on day 1 the correlations between the markers were weak or absent. This may suggest that the plasma half-lives of the markers are different. A temporary fall towards lower levels of the coagulation markers occurs during the first postoperative and posttraumatic days, but levels are above normal in the first week, suggesting continuing activation of coagulation. This may possibly reflect a secondary activation of the haemostatic system, promoted by the inflammatory processes in the wound healing sequence and procoagulant activity released when the haemostatic plugs are degraded. As indicated by increased levels of fibrin/fibrinogen degradation products, a secondary increase in fibrin degradation is observed between the 3rd and 7th days. This may reflect increased degradation of fibrin
as a response to the increased fibrin formation in this period, degradation of fibrin in the wound, and degradation of intravascular fibrin.

In the posttraumatic period the urinary excretion of fibrinopeptide A (FpA) is about 50-fold higher than in healthy controls with normal plasma levels of FpA. Likewise, prothrombin fragment 1+2 (F1+2) immunoreactivity is detected in the urine of trauma patients. The urinary immunoreactivity of F1+2 was higher than the corresponding plasma levels, and the excretion was almost 100 times that of healthy controls. This observation may suggest that the rate of fibrin formation was considerably higher than that indicated by plasma concentrations, which were only twice as high as normal.

The fall in plasma profibrinolytic activity (decreased t-PA activity/increased PAI activity) has previously been interpreted as decreased or impaired fibrinolysis after surgery and trauma. However, the author suggests that the fall in plasma profibrinolytic activity may be due to activation of plasmin by increased t-PA adsorption onto fibrin, resulting in increased fibrin degradation and lower plasma levels of t-PA.

The relationship between the occurrence of nonsymptomatic deep vein thrombosis (DVT) after surgery and haemostatic tests has been given much attention in the past. In the study by the author, levels of F1+2 and fibrin/fibrinogen degradation products were increased to a greater extent in patients in whom non-symptomatic DVT developed, as diagnosed by bilateral phlebography, than in patients without DVT.

In the study on trauma patients, a weak correlation was observed between the trauma score, assessed by the Injury Severity Score, and levels of the haemostatic markers, with the exception of the profibrinolytic markers (t-PA and PAI).

Levels of the haemostatic markers were not different when trauma patients who had received blood transfusions were compared with trauma patients who had no transfusions. On the other hand, posttraumatic levels of t-PA:ag and PAI-1:ag were higher in patients who had been transfused with 6 or more units of blood during resuscitation.

It was observed that 4 patients who developed posttraumatic pulmonary dysfunction (PD) had significantly lower levels of F1+2 and FbDP on the day after admission than patients without PD.

No clinical relevance of the haemostatic markers in surgery and trauma patients has yet been provided. On the other hand, the work by the author does not reject the hypothesis that the changes in the blood after surgery and trauma, as determined by the haemostatic markers, are a consequence of a dynamic haemostatic balance which is not only a local phenomenon, but is possibly a systemically activated condition with a subtle balance between intravascular formation and degradation of fibrin.

Previous experimental studies, autopsy studies, and paraclinical studies suggest that the pulmonary microvascular system clears the surplus production of fibrin microthromboemboli which follow after trauma and injections of tissue thromboplastin or thrombin. These fibrin thromboemboli may not promote tissue injury if they are cleared rapidly by the fibrinolytic system.

Both fibrin and fibrin degradation products have a potent permeability increasing effect on the pulmonary endothelial cells, and, in accordance with this, the early signs of posttraumatic pulmonary dysfunction are characterized by alveolar and interstitial œdema. Fibrin in the wound may activate the woundhealing sequence by activating the inflammatory system. It is suggested that intravascular fibrin deposition may result in a reaction similar to wound healing. The organ in which the intravascular fibrin clots are situated is mistaken for a wound by the inflammatory systems; this may lead to irreversible wound healing-like reactions and organ damage. Thus it may be suggested that the haemostatic balance after surgery and trauma is of significance for the balance between localized inflammation (wound healing) and disseminated inflammation (organ damage).

8 Summary in Danish

I de seneste år har udviklingen i immunologiske metoder gjort det muligt at konstruere analysemetoder, der er i stand til at måle spaltningssprodukter og enzyminhibitorkomplekser dannet ved aktivering af det hæmostatiske system. Det er foreslået, at metoderne kan kvantitere de forskellige enzymatiske reaktioner i det hæmostatiske system, og derved give et mere præcist billede af den aktuelle koagulations- og fibrinolysestatus end konventionelle koagulations- og fibrinolyseanalysemetoder.

Formålet med forfatterens arbejde har været at undersøge, hvorledes hoftealloplastikkirurgi, undrede kstremitetsfrakturer, kranietraumer og multitraumer påvirker koagulations- og fibrinolysestatus. Herudover er det forsøgt at finde mulige sammenhænge mellem det hæmostatiske system og kliniske fund og komplikationer efter kirurgi og traumer.

Udviklingen af og princippene for de forskellige koagulations- og fibrinolyseanalyse metoder gennemgås kort, og de af forfatteren fundne værdier hos raske personer samt analyserproducerbarhed indenfor de enkelte analyser angives. 


Kort efter et vævstrauze ses en god korrelation mellem de forskellige marker, men i løbet af det næste døgn ses en dårlig eller manglende korrelation
mellom de forskellige markører. Dette kunne tyde på, at halveringstiden for markørerne er forskellige efter traume.

I de efterfølgende 2-3 dage falder plasmaindholdet af koagulationsmarkører, men forbliver over normalområdet i de første uge, hvilket tyder på en kontinuerlig koagulationsaktivering i den postoperative/posttraumatiske fase.

Fra tredje til syvende dag ses en sekundær stigning af fibrinolysemarkører målt som degraderingsprodukter af fibrin og fibrinogen. Dette kunne tyde på en sekundær degradering af fibrin, hvilket kan være et udtryk for øget dannelse af fibrin i denne periode, nedbrydning af fibrin lokalisert i såret samt nedbrydning af intravaskulært lokalisert fibrin.

Efter multitraume falder plasmakoncentrationen af protrombin fragment 1+2 (F1+2) og fibrinopeptid A (FpA) til ca. det dobbelte af plasmakoncentrationen hos normale, hvorimod urinudskjellen af F1+2 og FpA er 50 til 100 gange højere hos traumapatienter end hos normale raske personer. Det fandtes en god korrelation mellem urinudskjellen og plasmakoncentrationen af F1+2. Disse resultater kunne tyde på, at koagulationsomstætningen er betydelig større hos disse patienter end hvad plasmakoncentrationen umiddelbart afslører.

Den profibrinolytiske aktivitet i plasma falder i løbet af det første døgn efter kirurgi og traumer (faldende t-PA aktivitet/stigende PAI aktivitet). Dette er konventionelt opfattet som udtryk for, at fibrinolysen er nedsat i det postoperative/posttraumatiske forløb.

Forfatteren foreslår, at den lave profibrinolytiske aktivitet i plasma kunne skyldes, at profibrinolytiske faktorer (t-PA) i plasma binder sig til fibrin og aktiverer plasmin, hvorved fibrinnebrydningen øges, men plasmaindholdet af profibrinolytiske faktorer falder.

Sammenhængen mellem forekomsten af dyb venøs trombose efter kirurgi og hæmostatiske test har gennem tiderne været genstand for stor interesse. I forfatterens undersøgelser sås en tendens til højere plasmakoncentrationer af F1+2 og fibrin/fibrinogen degraderingsprodukter hos patienter, som fik diagnosticeret ikke symptomgivende DVT ved flebografi sammenlignet med patienter med negativ flebografi.

I forfatterens undersøgelser på traumapatienter sås en svag korrelation mellem koagulations- og fibrinolysemarkører og traumestørrelsen beregnet med "The Injury Severity Score" (ISS), hvorimod de profibrinolytiske aktivatorer og inhibitorer ikke var korreleret til ISS.

Koagulations- og fibrinolysemarkørerne var ikke forskellige hos traumapatienter, som fik blodtransfusioner sammenlignet med traumapatienter, der ikke fik blodtransfusioner. Patienter, der under den primære behandling fik 6 eller flere blodtransfusioner, havde i den posttraumatiske fase højere plasmakoncentrationer af profibrinolytiske aktivatorer og inhibitorer (t-PA/PAI).

Hos patienter, der udviklede posttraumatiskt lungedysefunktion fandtes lavere værdier af F1+2 og fibrin degraderingsprodukter dagen efter traumaet. Herudover fandtes ingen forskelle i plasmakoncentrationen af de forskellige markører ved sammenligningen mellem patienter med og uden posttraumatiske lungen dysefunktion.

Forfatterens undersøgelser tyder på, at de hæmostatiske reaktioner efter væselslæsion er i en dynamisk og aktiveret tilstand, som ikke kun er et lokalt fænomen i området ved væselslæsionen, men formentlig en systemisk aktiveret reaktion med en hårfin balance mellem intravaskulære dannelse og nedbrydning af fibrin. Herudover har forfatterens undersøgelser ikke afsløret nogen klinisk anvendelighed af de hæmostatiske markører.

Tidligere eksperimentelle studier, autopsi studier og parakliniske studier tyder på, at lungen kredsløbet fjerner "overskudsproduktionen" af mikrotromboembolier, som umiddelbart efter traumer eller efter indgift af vævstriboplastin eller trombin føres til lungekredsløbet. Mikrotromboembolierne når formentlig ikke at gøre nogen skade, hvis det fibrinolytiske system er i stand til hurtigt at opløse dem.

Både mikrotromber og fibrin degraderingsprodukter har en betydelig permeabilitets øgende effekt på endotelcellerne i lungekredsløbet och i overensstemmelse hermed er det primære billede på posttraumatiske lungen dysefunktion præget af alveolært og interstitielt lungedøde.

Fibrin i såret aktiverer det inflammatoriske system og starter formentlig sårhelingsreaktionen. Det foreslås, at fibrinmikrotromboembolier lokaliseret i det mikrovaskulære kredsløb også er i stand til at aktivere sårhelingsreaktionen. D.v.s. at organismen fejlkender dette mikrovaskulære kredsløb som et sår (f.eks. lungen kredsløbet), og følgen kan i værste fald være en irreversible sårhelingsreaktion og organskade. Derfor foreslås det, at den dynamiske hæmostatiske balance efter kirurgi og traumer har betydning for balancen mellem lokaliseret inflammation (sårhelingsreaktion) og dissemineret inflammation (organskade).

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