Haemostasis during Infrarenal Aortic Aneurysm Surgery: Effect of Volume Loading and Cross-clamping

A. C. Vahl[1], A. J. C. Mackaay[1], P. C. Huijgens[2], G. J. Scheffer[3] and J. A. Rauwerda[1]

Department of [1]Vascular Surgery, [2]Haematology and [3]Anaesthesiology, Vrije Universiteit Hospital, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands

Objectives: To study thrombin and plasmin activation during elective abdominal aortic aneurysm surgery.
Design: Prospective study.
Setting: University Hospital.
Materials: Nine consecutive patients undergoing elective surgery were included. The mean age was 72 years (range 60–79). Blood samples were drawn: (1) before induction of anaesthesia; (2) after induction and Swan Ganz catherisation; (3) just before cross-clamping; (4) before declamping; (5) 8 h postoperatively; (6) 18 h postoperatively.
Chief outcome measures: Assays included: prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, prothrombin fragments (F 1 + 2), anti-thrombin III (ATIII), plasminogen, $\alpha2$-antiplasmin, haematocrit, platelet and serum protein for correction of haemodilution. Data were expressed as mean (s.D.). Differences between mean values were tested by means of the ANOVA for repeated measures and the Wilcoxon signed rank test.
Main results: The APTT and TT did not change until heparinisation. The F 1 + 2 were already elevated preoperatively. After correction for haemodilution the AT III and $\alpha2$-antiplasmin decreased in time (p = 0.009 and 0.0023, respectively) and the F1 + 2 increased (p < 0.0001). Postoperatively (t5 and 6) the values normalised again.
Conclusions: The coagulation and fibrinolytic systems are activated during and after elective aortic replacement. Standard tests, like the prothrombin and partial thromboplastin time, are unreliable when assessing the coagulation status of the patient.

Key Words: Aortic aneurysm; Fibrinolysis; Thrombin activation; Plasmin activation; Haemodilution.

Introduction

Aortic grafting for abdominal aortic aneurysm may be accompanied by major peroperative blood loss. Even after a surgical cause of bleeding has been eliminated a disturbance of the balance between coagulation and fibrinolysis may have developed causing a coagulopathy which can lead to generalised oozing and severe blood loss. It has been shown that perioperative coagulopathy in patients with a ruptured abdominal aortic aneurysm is a strong indicator of poor outcome.[1,2] It is well known that the aneurysm itself can be the cause of clotting disorders, like intravascular coagulation[3-9] which occurs in up to 4% of patients.[10] However, it is unknown whether other perioperative features contribute to coagulopathy. Besides adequate haemostasis, another major issue is adequate tissue perfusion. The circulation may be supported by infusion of fluids. Epidural analgaesia causes vasodilation necessitating volume replacement. All together these measures will lead to haemodilution, which may have an impact on the level and activity of coagulation and fibrinolytis factors.

The aim of this study was to determine whether, and when, thrombin and/or plasmin activation takes place in patients operated on for an abdominal aortic aneurysm. The impact of volume loading on the level and activity of clotting factors was also investigated.

Patients and Methods

Nine consecutive patients undergoing elective repair of infrarenal aortic aneurysms were included. The mean age was 72 years (range 60–79) and in all patients a preclotted tube or bifurcation graft of knitted Dacron was inserted.

A standardised anaesthetic procedure was performed. Patient were positioned on a heated mattress. Induction was performed with 0.01 mg sufentanil forte, 0.1 mg pancuronium, 0.2 mg etomidate and 1 mg dexamethason all per kg of body weight. During

induction of anaesthesia volume loading with NaCl 0.9% was performed at a rate of 10–20 ml/kg/h. Before cross-clamping patients were heparinised with 5000 IU of heparin. Anaesthesia was maintained with sufentanyl forte and midazolam. When necessary dopamine and nitroglycerine were added. Blood loss was compensated by NaCl 0.9%, autologous transfusion by use of the cell saver and units of homologous packed cells. Postoperatively patients were artificially ventilated until their circulatory and respiratory condition were stable.

Blood samples were aspirated from the radial artery on the following time (t) points: (1) before induction of anaesthesia; (2) after induction of anaesthesia and Swan Ganz catherisation; (3) during the operation before cross-clamping; (4) after insertion of the prosthesis and before declamping; (5) 8 h postoperatively; (6) 18 h postoperatively. Blood was drawn into plastic syringes and immediately transferred into 0.106 mmol/l trisodium citrate. Platelet poor plasma was prepared by centrifugation at 2000 g for 10 min and made platelet-free by a second centrifugation step (12000 r.p.m. for 3 min in an Eppendorf centrifuge). The prothrombin time (PT) and activated partial thromboplastin time (APTT) were automatically assayed, using Thromborel (Behringwerke, Marburg, Germany) and PTT (Boehringer, Mannheim, Germany), respectively. The fibrinogen level was determined using the method of Clauss. Antithrombin III was assayed with the chromogenic substrate S-2765 (Chromogenix, Molndal, Sweden). Plasminogen was

determined using S-2403 (Chromogenix) and a2-antiplasmin using S 2251 (Chromogenix). Prothrombin fragment 1 + 2 was assayed by an ELISA technique (Enzygnost, Behringwerke, Germany). All tests were performed according the guidelines of the manufacturers.

Blood was also transferred into EDTA prefilled tubes for conventional estimation of haematocrit and platelet count (Table 1). The serum total protein concentration (TP: g/l) was determined to permit a correction for haemodilution, by dividing the clotting parameters by this value. These corrected values for the haemostatic parameters are indicated as index numbers. For every time point the mean (S.D.) of the parameters was calculated. Differences between mean values were analysed by the ANOVA for repeated measures (BMDP version 7.0) and the Wilcoxon signed rank test. A p-value of less than 0.05 was considered statistically significant.

Results

The mean peroperative blood loss was 2500 ml (range 1100–9500 ml). In eight patients there was no major surgical bleeding and all patients remained stable perioperatively. The mean aortic cross-clamping time was 80 min (range 30–150).

The mean total protein concentration was initially 56 g/l (t1), and decreased by 34% to 37 g/l at t4 as a

Table 1. Routine laboratory tests and parameters of thrombin and plasmin formation during and after abdominal aortic aneurysm replacement. Values are given as mean (S.D.). For time points see materials and methods.

Parameters	Time points						Normal value
	1	2	3	4	5	6	
Haematocrit	0.45	0.36	0.31	0.29	0.33	0.33	0.40–0.50 1/1
	(0.06)	(0.03)	(0.03)	(0.06)	(0.06)	(0.06)	
Platelet	213	190	158	128	134	126	200–300 x$10^9$1
	(88)	(88)	(67)	(49)	(66)	(74)	
Total protein	56	50	43	37	48	48	40–60 g/l
	(8)	(6)	(5)	(4)	(5)	(5)	
PT	17	16	19	25	18	17	16±2 s
	(3)	(2)	(3)	(3)	(1)	(2)	
APTT	49	46	56	116	44	40	25–35 s
	(9)	(10)	(26)	(11)	(7)	(5)	
Fibrinogen	3.4	3.5	2.9	2.2	2.1	2.9	2–4 g/l
	(1.6)	(1.3)	(1.4)	(1.0)	(0.7)	(0.8)	
AT III	85	83	65	41	67	78	>80%
	(25)	(22)	(14)	(6)	(29)	(19)	
F 1 + 2	2.3	1.7	2.5	1.9	3.3	2.0	0.4–1.1 nnmol/l
	(1.4)	(0.8)	(1.7)	(1.1)	(1.5)	(1.0)	
Plasminogen	90	85	75	46	68	62	>70%
	(29)	(22)	(27)	(17)	(32)	(20)	
a2 antiplasmin	83	85	66	48	61	75	>70%
	(17)	(18)	(17)	(15)	(16)	(20)	

result of volume loading (t1–3) and blood loss (t2–4). The results of laboratory tests are shown in Table 1. The haematocrit and platelet count decreased (36% and 40% respectively) perioperatively. The APTT and PT were elevated at t4 due to routine use of heparin. The differences in these values during t1–3 were not statistically significant in contrast to the decrease in HT, platelet and TP. However, when the decrease in platelet was corrected for haemodilution, (Thr/TP) there remained a slight, but statistically insignificant decrease. When corrected for haemodilution the APTT and PT showed a slight, but insignificant increase between 1t and 3. However, these tests were of little use due to heparinisation of the patients.

Plasmin formation was estimated by changes in the level of plasminogen. This value decreased during the operation, however this decrease was not statistically significant for repeated measures (Fig. 1). Thrombin

formation was estimated by changes in fibrinogen and AT III level and especially by changes in the level of prothrombin fragment 1 + 2. F 1 + 2 levels were increased at the start of the operation and increased during and after the operation. However when corrected for haemodilution there was a highly significant increase perioperatively and a significant decrease one day after the operation (Fig. 2). The decrease in AT III was also statistically significant. (Fig. 3).

Figures 1–5 show the different parameters of thrombin and plasmin activation, corrected for haemodilution (index number). Most values show a slight, but insignificant, increase between t1 and t2. Five patients showed a decreased fibrinogen level at the end of the operation, which fell by one-third of the initial level. However this decrease was not statistically significant.
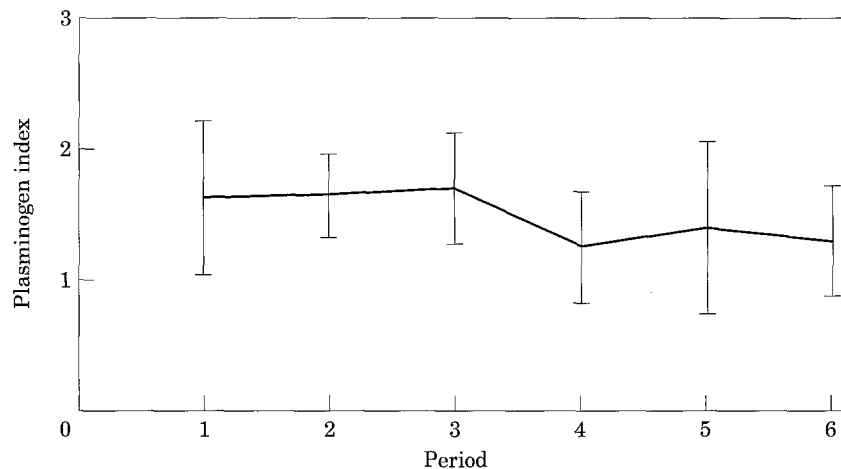

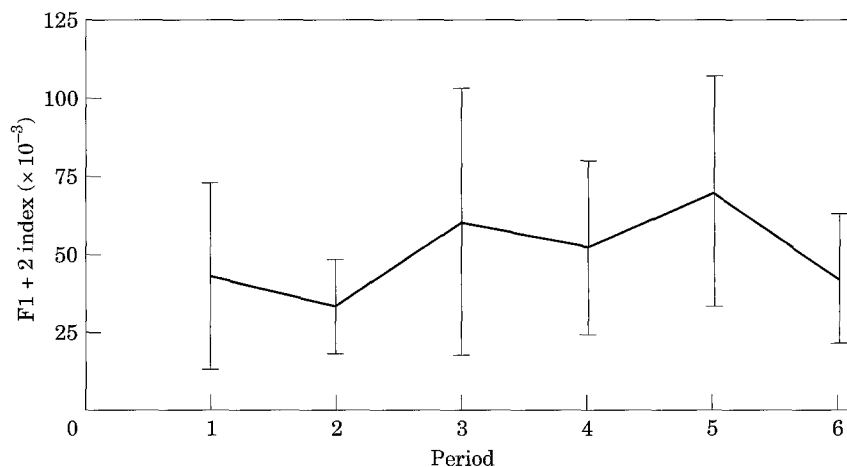Fig. 1. Plasminogen activity index p = 0.18 (ANOVA).

Fig. 2. F 1 + 2 concentration index p = 0.0000 (ANOVA); increase t1–t5 $p < 0.01$, decrease t5–t6 $p < 0.01$ (Wilcoxon).
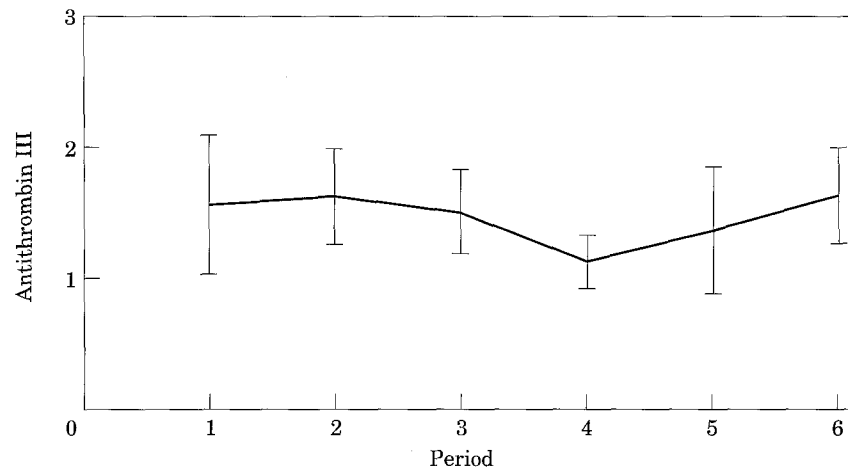
Fig. 3. Antithrombin III activity index $p = 0.009$ (ANOVA); decrease t1–t4 $p < 0.05$, increase t4–t6 $p < 0.02$ (Wilcoxon).

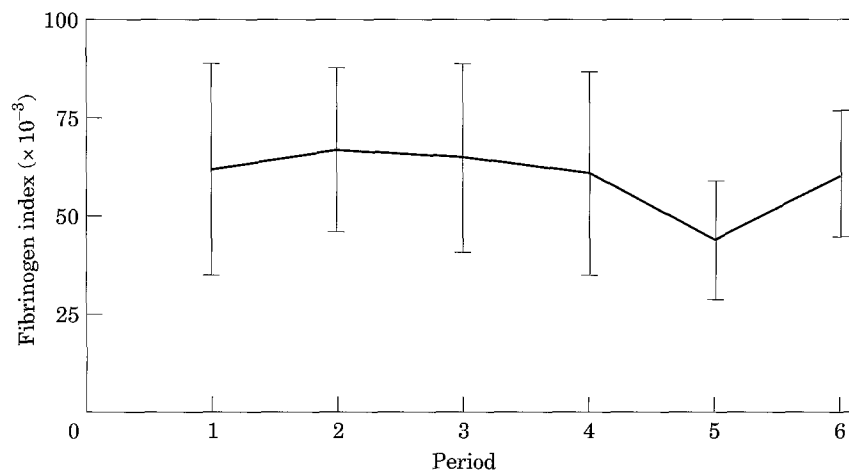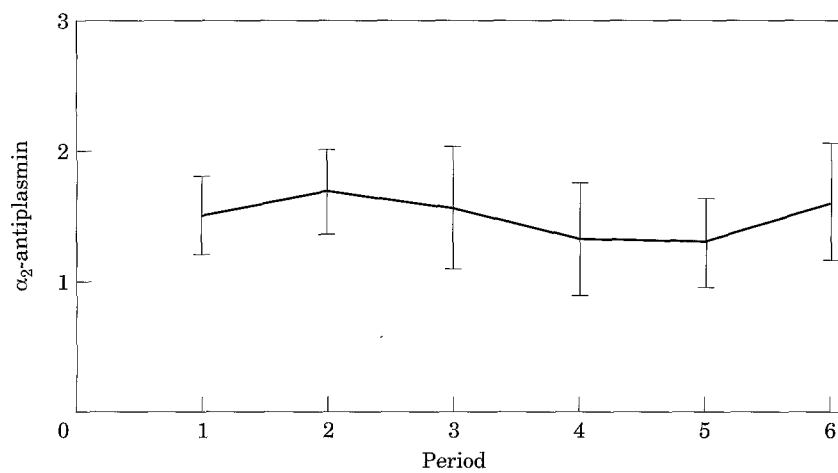**Fig. 4.** Fibrinogen index $p = 0.11$ (ANOVA).

Fig. 5. α2 antiplasmin activity index $p = 0.0023$ (ANOVA); decrease t2–t5 $p < 0.05$ (Wilcoxon).

Discussion

This study shows that replacement of an abdominal aortic aneurysm by a prosthesis is accompanied by activation of coagulation and fibrinolytic factors. Haemodilution, due to volume therapy, especially after declamping, influences the concentration of several components of the blood. The haematocrit, platelet and total protein concentration decreased during the operation as a result of haemodilution, as well as blood loss.

The APTT and PT did not change significantly during the operation except during cross-clamping (t4), because the patients were heparinised. The concentrations of fibrinogen, ATIII, plasminogen and α2 antiplasmin decreased during the operation and the concentration of F1 + 2 increased. These findings suggest both thrombin- and plasmin activation. However, they should be correlated with the dilution factor. After 18 h the parameters returned to their preoperative level except for plasminogen. In accordance with the literature, we showed a decrease in the levels of some haemostasis factors during the operation.[11,12] However, in contrast to our study, these studies did not correct for haemodilution, precluding the estimation of the impact of thrombin and plasmin generation. When the parameters are corrected for haemodilution, by dividing the value by the total protein concentration, the real consumption and generation of thrombin and plasmin activation can be calculated (= index number).

There was a relative decrease of the platelet index from a mean of 3.9 to 2.7. Decrease of platelets before aortic operations is well known and is especially seen in patients with ruptured aneurysm.[1] Platelet function is also decreased.[13] It has been shown that ulcerated plaques are responsible for platelet aggregation.[14] Decrease of platelet count ($< 100 \times 10^9/l$), combined with an increase in coagulation time is associated with a high mortality rate of 65–70%.[1,2] The syndrome of intravascular coagulation (consumption coagulopathy) has been described in patients with an aortic aneurysm.[5,8,15] This entity is characterised by a low platelet count, low fibrinogen level, elevated fibrin degradation products (FDP) and prolongation of one or more coagulation function tests.[15] Our patients showed an overall increased F 1 + 2 level preoperatively, suggesting that there was a low level of thrombin activation preoperatively. We did not measure FDP in our patients, because the level of FDP is influenced by many factors not relevant for this study. Three patients in our series had a decreased fibrinogen level ($< 2 g/l$) preoperatively (t1) while other criteria of intravascular coagulation were absent. Five patients

had decreased fibrinogen levels perioperatively (t4). When the correction for haemodilution was calculated the mean loss of fibrinogen was one-third of its initial level.

The thrombin activation system was induced: the ATIII index decreasing from a mean of 1.55 to 1.10 from t1 to t4. Whether this decrease was completely due to heparin (ATIII binding) remains to be resolved.[16,17] The mean decrease in our patients was 25% within a few hours. In the literature a decrease of 30% has been reported after 3–5 days of continuous infusion of heparin.[18] There is at least a non-heparin induced effect during the operation. The index of F 1 + 2 increased from 41 to 64 perioperatively, indicating thrombin activation. At t6 this level had only normalised in three patients ($< 1.1 nmol/l$). However the mean value had returned to the preoperative level. It should be noted that the increase of F 1 + 2 had already started at t3 after the insertion of the Swan Ganz catheter, which may be a causative factor. As a result of an activated coagulation cascade, the fibrinolytic cascade is also activated. Plasmin, split from plasminogen, decreased perioperatively. The concentration index of α2 antiplasmin is decreased from 1.7 at, period 2 to 1.2 at period 5. In contrast to the plasminogen level, which remained low, the level of this inhibitor increased again to preoperative values. This could be due to rapid synthesis of this protein or is it an early indicator of normalisation of haemostasis?

Haemostasis can be disturbed by several factors. It is proven that the aneurysm itself can be the cause due to local consumption.[8,15] However it is likely that the inserted prosthesis and other intravenous devices, like the Swan Ganz, can also cause an induction of the coagulation and fibrinolytic cascade. Reperfusion of the intestines and lower extremities may contribute to fibrinolysis, while it has been shown that endotoxin and interleukin I, which are released by ischaemic intestine during cross-clamping, can interfere with the endothelial cell function resulting in induction of coagulation and fibrinolysis.[19,20] Colon ischaemia during the operation can result in intravascular coagulation.[21] Hypoxia combined with reperfusion induces procoagulant activity.[22]

Haemodilution caused an overall decrease in the coagulation and fibrinolysis factors of 50%. However, activation of the thrombin and plasmin cascade resulted in a loss of 25% of the initial activity, but the levels normalised again. The synthesis of coagulation factors was not taken into account in our study. About 10% of the platelet count is produced within 1 day and proteins can be synthesised within 8 h. So if we make a correction for new formation and synthesis of

clotting parameters, the peroperative decrease would be even more significant. Even with a normal APPT and PT, diffuse oozing from the retroperitoneum and the wound are frequently observed, probably because subtle parameters of the coagulation system are disturbed. Disturbance in the fibrinolytic system is especially difficult to assess. Therefore it may be reasonable to influence the fibrinolytic system by medication. It has already been shown that aprotinin has a beneficial effect on the amount of blood loss by antagonising fibrinolysis.[23-25]

In conclusion, in patients undergoing repair of an abdominal aortic aneurysm, coagulation and fibrinolytic systems are activated during and after elective aortic replacement. Several factors are disturbed due to haemodilution, consumption and activation. Standard tests like the PT and APTT time are unreliable when assessing the coagulation status of the patient.

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