



ACTIVATION OF THE HEMOSTATIC PROCESS IN PATIENTS WITH UNRUPTURED AORTIC ANEURYSM BEFORE AND IN THE FIRST WEEK AFTER SURGICAL REPAIR

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ABSTRACT

Background and Objective. It has been previously suggested that activation of coagulation and fibrinolysis may sometime occur in patients with unruptured aortic aneurysm. However, the incidence of this complication and the effect of surgical repair are unknown. The objective of our study was to gain further information on this topic.

Methods. We investigated activation of the hemostatic process in 20 consecutive patients with unruptured abdominal aortic aneurysm. We then evaluated the effect of surgical repair of the vascular abnormalities.

Results. Both before and in the first week after surgery, the large majority of patients showed clear signs of activation of coagulation (increased plas-

ma levels of prothrombin fragment 1+2 and fibrin peptide A), and many had low levels of the natural anticoagulant antithrombin III. Platelets were activated in all cases (high levels of plasma beta-thromboglobulin), and signs of platelet consumption (thrombocytopenia and/or increased mean platelet volume) were present in most of them.

Interpretation and Conclusions. Activation of the hemostatic process occurs in nearly all patients with abdominal aortic aneurysm and could play a role in the hemorrhagic and thrombotic events that can complicate the clinical development of these subjects.

Key words: aortic aneurysm, hemostasis, coagulation, platelets, fibrinolysis

Although some case reports have documented the rare association of aortic aneurysmal disease and disseminated intravascular coagulation,¹⁻³ few investigations have been directed towards the study of activation of the hemostatic process in this condition.⁴⁻⁷

Moreover, most of these studies were performed years ago, before sensitive laboratory tests for the activation of platelets, coagulation and fibrinolysis were available.

Activation of hemostasis could be clinically relevant in these patients as they have an increased risk of both bleeding and thrombosis, especially in the perioperative course of surgical repair of their vascular abnormalities.⁸

To gain further information about this subject, we studied some hemostatic parameters in 20 consecutive patients with abdominal aortic aneurysm before and at different times after surgical repair with a Dacron graft.

Our results show systemic thrombin formation and platelet activation in nearly all patients both before and in the first week after intervention, although none of them presented clinical symptoms of consumptive coagulopathy.

Patients and Methods

Patients

A prospective study was carried out on 20 consecutive patients (19 males and one female; mean age 69.8 years) undergoing elective repair of unruptured aortic aneurysm. Informed consent for taking part in the study was obtained. All patients had normal liver function and none of them required plasma or platelet concentrates during surgery or in the following week. Anticoagulant therapy with subcutaneous heparin calcium was started the day before surgery (12,500 IU) and continued for the entire length of the study (5,000 IU every 8 hours). During surgery, additional systemic anticoagulation with heparin (5,000 IU) was given prior to aortic clamping. Dacron grafts were used for aortic repair according to the *inlay technique*. The post-operative course was uneventful in 15 cases; two patients underwent reoperation for hemorrhage control and three for leg ischemia.

Laboratory analysis

Laboratory investigation of hemostasis was performed on the day prior to surgery (before the start of heparin therapy), and one and 7 days after

surgery. Platelet count (plt, normal range: 150-400 $\times 10^9/L$) and mean platelet volume (MPV, normal range: 8.5-10.5 fL) were measured in K_3EDTA (1.5 mg/mL) anticoagulated blood samples (using a Sysmex NE8000 cell counter, Toa Medical Electronics, Carson, CA, USA) within 30 minutes of blood sampling; previous experiments have shown that MPV does not change significantly during this time.⁹ The coefficient of variation in MPV values obtained from ten consecutive analyses of the same normal sample was quoted by the manufacturer as being less than 3%.

Normal ranges of other laboratory tests were as follows: activated partial thromboplastin time (aPTT): 25-40 sec. (Pathromptin, Behring, Marburg, Germany); prothrombin time (PT) ratio: ≤ 1.2 (Thromborel S, Behring); plasma fibrinogen (Fbg): 180-400 mg/dL (Multifibren, Behring); β -thromboglobulin (β -TG): 10-40 IU/mL (ELISA β TG, Boehringer-Mannheim, Mannheim, Germany); prothrombin fragment 1+2 (F1+2): 0.44-1.11 nM (Dade Prothrombin fragment F1.2 Elisa, Baxter, Lessines, Belgium); fibrin peptide A (FPA): < 3 ng/mL (ELISA-FPA Boehringer); antithrombin III (ATIII): 75-125 U/dL (Behrichrome ATIII, Behring); d-dimer of cross-linked fibrin degradation products (D-D): < 0.5 mg/L (Immunoassay Nycocard D-D dimer, Nycomed Pharma, Oslo, Norway). The following anticoagulants were utilized according to manufacturer's instructions: ATIII, aPTT, PT, Fbg, D-D: sodium citrate; β -TG: CTAD; F1.2: heparin; FPA bentonit.

Statistical analysis

The differences between groups were analyzed using ANOVA and Scheffé tests or the χ^2 test. All the values observed in 30 healthy, age- and gender-matched control subjects represented normal ranges of investigated parameters.

Results

The results of laboratory tests performed before and at different times after aortic aneurysm repair are shown in Table 1.

Before surgery, the traditional coagulation parameters showed only minor abnormalities: a few patients had a slightly prolonged aPTT, but none showed defective PT ratios or low fibrinogen levels. On the contrary, high values of this protein were observed in 7 of the 20 cases. At the preoperative baseline reading, nearly all patients showed increased molecular markers of coagulation activation: 19 of the 20 subjects presented clear signs of thrombin formation (elevated F1+2) and/or thrombin-induced cleavage of fibrinogen (elevated FPA). Moreover, high levels of D-D (indicative of fibrin formation) were observed in all patients, and low levels of the natural anticoagulant ATIII were found in 10 cases. At the baseline, very high plasma levels

of β -TG, an α -granule protein secreted in the plasma by activated platelets, were observed in all cases; 5 patients also showed mild thrombocytopenia and 11 showed elevated MPV.

The day after surgery, the number of subjects with abnormal platelet count, abnormal aPTT or PT ratio was significantly increased; however, six days later the number of thrombocytopenic patients was reduced compared to baseline, while the number of subjects with high fibrinogen levels was increased. Aside from a decrease in F1+2, surgical repair of the aortic aneurysm had little effect on the parameters indicative of hemostatic activation in the first postoperative week.

Discussion

Although disseminated intravascular coagulation is a rare event in patients with unruptured aortic aneurysm, it is now recognized that activation of coagulation and fibrinolysis is a frequent characteristic of such subjects.⁷

Table 1. Hemostasis investigation in 20 patients undergoing surgical repair of abdominal aortic aneurysm.

	Normal range	Pre	Post1	Post7
Platelet count ($\times 10^9/L$)	150-400	186 (63)	146 (59)*	225 (69)* ^o
Abnormal value		5	12*	2* ^o
Mean platelet volume (fL)	8.5-10.5	10.8 (1.0)	10.9 (1.1)	10.5 (0.8)
Abnormal value		11	10	11
β -thromboglobulin (UI/mL)	10-40	219 (22)	209 (38)	216 (18)
Abnormal value		20	20	20
aPTT (sec.)	25-45	36.9 (10.2)	38.1 (8.4)	34.0 (7.3) ^o
Abnormal value		3	8*	3 ^o
Prothrombin time ratio	≤ 1.2	1.06 (0.06)	1.2 (0.1)*	1.12 (0.16) ^o
Abnormal value		0	7*	1 ^o
Fibrinogen (mg/dL)	180-400	328 (80)	321 (73)	472 (55)* ^o
Abnormal value		7	6	16* ^o
F1+2 (nM/L)	0.44-1.11	2.4 (1.1)	2.0 (1.0)*	1.8 (0.8)* ^o
Abnormal value		18	18	15
Fibrin peptide A (ng/mL)	≤ 3.0	18.3 (13.9)	22.7 (13.0)	23.0 (13.3)
Abnormal value		19	20	20
Antithrombin III (%)	75-125	75 (27)	72 (25)	70 (21)
Abnormal value		10	10	11
D-D (mg/L)	≤ 0.5	4.6 (2.5)	4.8 (2.7)	4.9 (2.6)
Abnormal value		20	20	20

Values of laboratory investigations are mean values (standard deviation). The number of patients with abnormal values is also reported. Pre, preoperative day; Post, postoperative day; aPTT, activated partial thromboplastin time; F1+2, prothrombin fragment 1+2; D-D, d-dimer of cross-linked fibrin degradation products. * $p < 0.05$ with respect to Pre; ^o $p < 0.05$ with respect to Post1.

The present study confirms and extends these results by demonstrating that systemic activation of coagulation is a constant feature in these patients and that platelets are also involved in this phenomenon. In fact, all 20 of the subjects investigated showed positive markers for increased thrombin formation and/or thrombin-induced cleavage of fibrinogen; in addition, the high D-D levels observed in all patients confirmed fibrin formation. Although only 5 patients presented thrombocytopenia, the high MPV observed in 11 of the 20 cases indicated that accelerated platelet turnover was occurring in the majority of them, since it has been shown that increased MPV causes accelerated platelet production¹⁰ and may be interpreted in the same way as a reticulocyte count. Furthermore, all subjects had a high plasma concentration of β -TG, indicating that a large number of platelets were undergoing release reaction. On the basis of these results, we suggest that platelet activation was present in all cases, and that compensated or uncompensated platelet consumption occurred in the majority of them. Hanson *et al.*¹¹ showed that platelet survival in patients with abdominal aortic aneurysm was shorter than expected based on platelet incorporation by the aneurysms, and concluded that an additional, unrecognized component of platelet destruction was operative in this disorder. Our observation that systemic thrombin formation and platelet activation are constant features of subjects with aortic aneurysm could offer an explanation for this phenomenon.

Our results only seemingly differ with previous studies that showed a lower incidence of activation of the hemostatic process in patients with unruptured aortic aneurysms.⁴⁻⁷ In our opinion, there is little doubt that these discrepancies are due to the different sensitivity of the laboratory tests available at the time when these earlier studies were performed. In fact, traditional coagulative tests and platelet count were also normal in many of our patients, while more sensitive markers of activation of coagulation and platelets were extremely positive.

Aside from a transient decrease in platelets and coagulation factors due to consumption during surgery, aortic aneurysm repair and heparin therapy had little effect on hemostatic parameters in the first postoperative week, i.e. clear signs of activation of platelets and coagulation were still present at one and 7 days after surgery. The significant

increase of platelets and fibrinogen at day 7 does not contradict this conclusion, since these changes are thought to reflect a general physiological response to surgical trauma or an inflammatory response.^{12,13}

The fact that aorta repair did not have a prompt effect on hemostatic parameters is not surprising, since the thrombogenic surface of the aneurysm was replaced by the surface of the Dacron graft, which is known to remain thrombogenic for a long period.¹⁰ In addition to this, the low levels of the natural anticoagulant ATIII observed in many patients may have played a role in the delay of coagulation normalization.

In conclusion, our observation suggests that activation of coagulation and platelets is a constant characteristic of patients with aortic aneurysm both before and in the first week after elective abdominal aortic surgery. This phenomenon could play a role in the thrombotic events that can complicate the clinical development of these patients.

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