

# Perioperative Activation of Hemostasis in Vascular Surgery Patients

Charles Marc Samama, M.D., Ph.D.,\* Dominique Thiry, M.D.,† Ismael Elalamy, M.D., Ph.D.,‡  
Mohamed Diaby, Ph.D.,§ Jean-Jacques Guillosson, Ph.D.,|| Edouard Kieffer, M.D.,# Pierre Coriat, M.D.\*\*

**Background:** Perioperative activation of hemostasis could play an important role in the occurrence of postoperative cardiac events. The authors conducted a prospective study to assess platelet function, coagulation, and fibrinolysis status during and after infrarenal aortic surgery.

**Methods:** Seventeen patients were studied. Excluded were patients with preoperative coagulopathies or liver disease, or cardiac or renal insufficiency; patients receiving anticoagulant treatment, antiplatelet agents, nonsteroidal antiinflammatory agents, fresh frozen plasma, or platelet concentrates; and patients undergoing reoperation and septic patients. Blood samples were drawn before induction (T1), 1 h after incision (T2), 1 h after extubation (T3), 24 h postoperatively (T4), 48 h postoperatively (T5), and at day 7 (T6). The following tests were performed: platelet count, platelet aggregation, platelet flow cytometry for CD62 and CD63, usual coagulation tests, thrombin-antithrombin complexes, plasminogen activator inhibitor 1.

**Results:** A significant increase of adenosine diphosphate-induced platelet aggregation was observed postoperatively at T4 and T5. This was not associated with a change of flow cytometry profile. No increase of thrombin-antithrombin complex levels was observed. A higher fibrinogen rate was detected at T5 and T6. Greater amounts of plasminogen activator inhibitor 1 were detected at T3 and T4. Thus, thrombin generation was limited and fibrinolysis was impaired postoperatively. Platelets were not activated in the postoperative period, as shown by flow cytometry, but were prone to be activated, as shown by aggregation studies.

**Conclusion:** The association of more easily activated platelets with a higher fibrinogen rate and a temporary shut down of fibrinolysis during the early postoperative period may indicate an increased thrombotic risk in patients undergoing major vascular surgery.

EXTENSIVE changes in the plasma levels of coagulation factors and in thromboelastographic parameters leading to an hypercoagulable state have been observed after

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\* Assistant Professor, Department of Anesthesiology, Avicenne Hospital.  
† Research Fellow, \*\* Professor and Chairman, Department of Anesthesiology,  
‡ Pharmacist, || Professor and Chairman, Emergency Biology Laboratory,  
# Professor and Chairman, Department of Vascular Surgery, La Pitié-Salpêtrière Hospital.  
‡ Assistant Professor, Laboratory of Hematology, Hôtel-Dieu Hospital.

Received from the Department of Anesthesiology, Centre Hospitalier Universitaire Avicenne, Université Paris 13, Bobigny, France; the Department of Anesthesiology and Emergency Biology Laboratory, Centre Hospitalier Universitaire Pitié-Salpêtrière, Université Paris 6, Paris, France; and the Laboratory of Hematology, Centre Hospitalier Universitaire Hôtel-Dieu, Université Paris 6, Paris, France. Submitted for publication December 8, 1999. Accepted for publication July 26, 2000. Support was provided solely from institutional and/or departmental sources. Presented in part at the 6th Congress of the European Society of Anaesthesiologists, Barcelona, Spain, April 25-28, 1998.

Address reprint requests to Dr. Samama: Département d'Anesthésie-Réanimation, Hôpital Avicenne, 125, route de Stalingrad, 93009 Bobigny cedex, France. Address electronic mail to: cmsamama@invivo.edu. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

abdominal aortic surgery.<sup>1,2</sup> Furthermore, an impairment in postoperative fibrinolysis has been reported by Rosenfeld *et al.*<sup>3</sup> in vascular surgery patients. Over the past decades, numerous studies<sup>4-6</sup> have reported an increased platelet response in patients with ischemic heart disease or peripheral vascular disease, but very few studies have focused on platelet function specifically during the perioperative period. Still, platelets play a key role in the pathogenesis of postoperative arterial occlusive disorders.<sup>7</sup> They become highly reactive as a result of shear stress, release of activating mediators, or a vessel damage. Platelet adhesion, granular release, and aggregation are thus induced. Platelet surface catalyzing coagulation reactions could also facilitate major thrombin generation. Together, these events promote thrombus formation and may therefore lead to arterial occlusion. Platelet function is generally only assessed by a conventional test, *i.e.*, platelet aggregation.<sup>8</sup> Indeed, this test provides valuable information regarding platelet reactivity, but bias has to be considered: *in vitro* platelet aggregation is artificially induced by an agonist, and no information is available on the resting platelet status.

Several monoclonal antibodies against platelet surface antigens have been developed.<sup>9</sup> Among them, antibodies recognizing activation-specific antigens such as CD62 (an internal  $\alpha$ -granule membrane protein (GMP-140, P-selectin), and CD63, a lysosomal integral membrane protein, can be used for detecting circulating activated platelets by flow cytometry. This method enables a much more specific approach to platelet status and has never been used postoperatively in vascular surgery to assess such a potential activation. Thrombin generation also plays a major role in the postoperative setting.<sup>1,7</sup> It can be evidenced by conventional coagulation tools and thrombin-antithrombin complex (T-AT) concentration. Fibrinolysis impairment was also described and may be involved in the occurrence of postoperative hypercoagulable state.<sup>3</sup> We conducted a prospective study to assess platelet function, coagulation, and fibrinolytic status during the perioperative period in patients scheduled for abdominal aortic replacement.

## Methods

This study was conducted in accordance with the Helsinki Declaration, European Good Clinical Practice, and French law. The protocol was approved by the ethical committee of La Pitié-Salpêtrière Hospital (Paris, France), and written informed consent was obtained from all patients.

Seventeen patients scheduled for infrarenal abdominal aortic replacement were included in the study. Excluded were patients with preoperative coagulopathies or liver disease, or with cardiac or renal insufficiency; those receiving anticoagulant treatment, antiplatelet agents, nonsteroidal antiinflammatory agents, fresh frozen plasma, or platelets concentrates; and patients undergoing reoperation and septic patients. Cardiac medications administered long term, except angiotensin-converting enzyme inhibitors, were given on the morning of surgery. All patients had an intraarterial catheter for arterial blood pressure measurements and blood sampling. Pre-medication with a benzodiazepine was allowed if necessary. Anesthesia was induced by propofol, sufentanil, and atracurium and was maintained with oxygen, nitric oxide, and isoflurane.

A 50-IU/kg bolus dose of unfractionated heparin was systematically injected intravenously immediately before aortic cross-clamping. Postoperatively, deep vein thrombosis prophylaxis was secured by a daily subcutaneous injection of 3,075 Anti Xa IU low-molecular-weight heparin (nadroparin; Fraxiparine, Sanofi, Gentilly, France). The first injection was given on day 1 in the evening (6 PM). Measured blood loss, fluid loading, and transfusion requirements (autologous and homologous erythrocyte units, cell salvage units) were recorded.

Blood samples were drawn on six occasions: before induction (T1), 1 h after incision (T2), 1 h after extubation in the recovery room (T3), 24 h postoperatively (T4), 48 h postoperatively (T5), and at day 7 (T6). Blood was sampled using the radial catheter at T1–T4 and from an antecubital vein at T5 and T6. Blood samples were collected in 3.8% trisodium citrated tubes (9:1 vol/vol, Becton Dickinson–France, Le Pont de Claix, France) for aggregometry and flow cytometry studies, prothrombin time, activated partial thromboplastin time, thrombin time (TT), fibrinogen, T-AT, and plasminogen activator inhibitor 1 (PAI-1), and in EDTA tubes (Becton Dickinson) for platelet count and hematocrit determinations. To prevent artifactual platelet activation and heparin contamination, 20 ml of blood was first slowly and smoothly sampled and discarded, and then blood samples were collected. All tests were performed at each step of measurement except for TT, T-AT, and PAI-1 at T6.

#### Platelet Aggregation

Platelet aggregation analysis (Pack 4-Platelet aggregation chromogenic kinetic system; Helena Laboratories, Beaumont, TX) was performed *ex vivo* on citrated platelet-rich plasma (PRP) and calibrated with autologous platelet-poor plasma (PPP). PRP was obtained after centrifugation of whole blood (200g, 10 min, 37°C). PPP was prepared from the same blood sample after centrifugation (1,500g, 20 min, 24°C). Platelet aggregation was induced by adenosine diphosphate 2.5 and 5  $\mu\text{M}$  and by arachidonic acid 500  $\mu\text{g}/\text{ml}$  (Helena–France, St. Leu,

France). The increase in light transmission was recorded for 4 min after the addition of the aggregating agent (agonist). Agonist-induced aggregation was evaluated in PRP by measuring the variation of light transmission, assuming that light transmission was 100% in PPP and 0% in unstimulated PRP.

The maximal intensity of platelet aggregation was defined as the maximal increase of light transmission, and velocity of platelet aggregation (slope of the curve) was defined as the speed of the increase in light transmission after agonist addition.

#### Platelet Flow Cytometry

The procedure for *ex vivo* detection of activated platelets has been described by Bihour *et al.*<sup>10</sup> Citrated blood was collected in polystyrene tubes containing paraformaldehyde 0.1%. Antibodies directed against P-selectin (CD62) and against lysosomal integral membrane protein (CD63) were obtained from Immunotech-Coulter, (Coultronics-France, Margency, France). After 1-h incubation with antibodies and fluorescein isothiocyanate conjugate, samples were diluted with 1 ml HEPES buffer and analyzed using a FacScan flow cytometer (Becton Dickinson). Fluorescence histograms were obtained for 10,000 cells, and data analysis was performed using Lysis II software (Becton Dickinson). Antibody binding was expressed as the percentage of platelets positive per category of antibody. Mean fluorescence intensity (arbitrary units converted to a linear scale) was a measure of the extent of antibody binding to individual platelets.

#### Coagulation Tests

Platelet-poor plasma was prepared after centrifugation (1,500g, 20 min, 20°C). Activated partial thromboplastin time, prothrombin time, TT tests, and fibrinogen levels were performed with a Hemolab automat (Biomerieux, Marcy l'Etoile, France). Activated partial thromboplastin time was determined with Actin FSL Dade reagent (Dade Behring France, Paris-La Défense, France), prothrombin time with Isimat Thromboplastin (Biomerieux), TT with Thrombicalci-test (Biomérieux), and fibrinogen with Thrombine Fibrinomat<sup>®</sup> (Biomérieux). T-AT levels were evaluated by an enzyme-linked immunosorbent assay using an Enzygnost T-AT micro kit (Dade Behring France).

#### Fibrinolysis

Plasminogen activator inhibitor 1 levels were measured using an enzyme-linked immunosorbent assay kit (Asserachrom-PAI-1; Diagnostica Stago, Asnières, France).

#### Statistical Analysis

Data are expressed as median (range) for blood loss, volume loading, and transfusion parameters (table 1). Values are expressed as mean  $\pm$  SD for all other param-

**Table 1. Intraoperative and Postoperative Bleeding, Fluid Loading, and Transfusion**

	Intraoperative	Postoperative
Blood loss (ml)	1,100 (500–5,000)	300 (0–1,050)
Gelatin (ml)	2,500 (1,000–5,000)	0 (0–2,000)
6% Hydroxyethyl starch, 200,000/0.5 (ml)	0 (0–1,500)	0 (0–1,500)
Ringer's lactate (ml)	1,500 (500–2,500)	500 (0–3,000)
Autologous RBC (units)*	0 (0–4)	0 (0–2)
Homologous RBC (units)*	0 (0–3)	0 (0–2)
Cell salvage units (units)*	1 (0–4)	—

Values are expressed as medians (extremes).

\* 1 unit  $\approx$  200 ml.

RBC = red blood cells.

eters. Median values were compared using the Mann-Whitney U test. Mean values were compared using analysis of variance for repeated measurements followed by a Scheffé test. *P* values less than 0.05 were required to reject the null hypothesis. Statistical analysis was performed on a computer using Statview SE Graphics (Abacus Concepts, Berkeley, CA).

## Results

Seventeen patients were included in the study (15 men, 2 women). The mean age was  $67 \pm 11$  yr, and the mean body weight was  $75 \pm 11$  kg. The mean aortic cross-clamping duration was  $48 \pm 22$  min. Intraoperative and postoperative bleeding, fluid loading, and blood transfusion are reported in table 1. No major bleeding was observed. No massive transfusion was required.

The preoperative values of all parameters were within the normal range. A significant increase in adenosine diphosphate-induced platelet aggregation was observed postoperatively at T4 and T5 (table 2). These features were not associated with a modification in flow cytometry profile either with CD62 and CD63. Platelet count increased significantly lately at T6 (table 2).

Activated partial thromboplastin time and TT were increased beyond the upper measurable value at T2 related to the heparin injection. A significant increase in fibrinogen concentration was measured at T5 and T6. No increase in T-AT level was recorded at any time. Conversely, a significant decrease of T-AT complexes was observed at T2.

A significant but temporary inhibition of fibrinolysis was observed at T3 and T4, as indicated by an increase in PAI-1 levels. PAI-1 returned to initial value at T5 (table 3).

## Discussion

Patients undergoing major vascular surgery are at high risk for developing coronary ischemic syndromes, transient ischemic cerebral attacks, or lower-extremity vascular occlusion.<sup>11–13</sup> This study was undertaken to inves-

tigate platelet status, thrombin generation, and fibrinolysis during and after abdominal aortic replacement. Except for T-ATs, which remained stable, all the results of this study emphasize the existence of a global hypercoagulable state in these patients during the early postoperative period.

Platelets play an important role in the pathogenesis of arterial diseases. Numerous studies have reported an increased platelet response in patients with atherosclerosis and ischemic vascular episodes.<sup>4–6</sup> Several tools exploring platelet functions have been proposed: platelet aggregation with various agonists, biochemical assays of granular released products ( $\beta$ -thromboglobulin, platelet factor 4, and thromboxane B2 metabolites), and more recently flow cytometric measurements of activated platelet-surface markers (glycoprotein IIb/IIIa, P-selectin).<sup>4,5,9,14–16</sup>

Rinder *et al.*<sup>16</sup> studied platelet activation during cardiopulmonary bypass using flow cytometry and a monoclonal antibody directed against P-selectin (CD62) which is expressed on the outer membrane surface after platelet activation. These investigators have also compared CD62 expression with conventional platelet aggregation assays in response to only one agonist, adenosine diphosphate. They showed that platelets were activated during and after cardiopulmonary bypass. The aim of their study was to underline the role of a potential platelet dysfunction in the occurrence of postoperative bleeding. However, no study has investigated the platelet response comparing aggregometry with flow cytometry parameters during and after major vascular surgery.

In our study, platelets were not activated intraoperatively and postoperatively as shown by flow cytometry but were prone to be activated with an increased functional response observed during the aggregation study. This is the first time that such a phenomenon has been evidenced. Flow cytometry could be understood as a kind of instantaneous picture of the platelet status. Conversely, platelet aggregation gives an indication of platelets' ability to respond, and this capacity can only be evaluated after agonist addition to PRP. Therefore, these platelet aggregation results showed that the degree of *in vitro*-induced platelet aggregation was more important postoperatively as compared with the preoperative status of these vascular surgical patients. This is a major point indicating that, postoperatively, any minor stress could activate platelets. Therefore, platelet prevention may be advisable, leading to the continuation of an eventual preoperative antiplatelet treatment or the initiation of such a treatment immediately after surgery in this vascular context. Aspirin or other nonsteroidal anti-inflammatory agents could inhibit this platelet hyperactivity and therefore potentially protect these patients against thrombotic events.<sup>17–20</sup> Furthermore, recent recommendations of the 5th Consensus Conference of the American College of Chest Physicians have emphasized

**Table 2. Platelet Activation Parameters**

	T1	T2	T3	T4	T5	T6
Platelet count (giga/l)	210 ± 61	186 ± 69	174 ± 60	163 ± 43	156 ± 52	340 ± 105*
AA <sub>max</sub> (%/normal)	96 ± 29	98 ± 45	101 ± 67	145 ± 85	137 ± 75	100 ± 12
ADP <sub>max</sub> (%/normal)	103 ± 29	112 ± 38	104 ± 33	120 ± 29*	127 ± 28*	93 ± 22
CD 62 (%/control)	96 ± 38	75 ± 14	71 ± 16	77 ± 15	92 ± 30	70 ± 07
CD 63 (%/control)	133 ± 41	123 ± 31	112 ± 26	123 ± 26	119 ± 32	108 ± 35

Values are mean ± SD. For platelet aggregation, values are expressed as percent of normal values defined previously in the laboratory in healthy volunteers with adjusted platelet counts. CD 62 and CD 63 are expressions of mean fluorescence intensity (arbitrary units converted to a linear scale; percentage of the control value (T1); each patient is his or her own control). CD 62 and CD 63 expressions at T1 differ from 100% because of the analytical variation of the method (2 aliquots) and of the heterogeneity of the size of the platelet population. Six points of measurements were defined: before induction (T1), 1 h after incision (T2), 1 h after extubation (T3), 24 h postoperatively (T4), 48 h postoperatively (T5), and at day 7 (T6).

\* *P* < 0.05 versus T1.

AA<sub>max</sub> = maximum intensity of arachidonic acid-induced platelet aggregation; ADP<sub>max</sub> = maximum intensity of 5 μM adenosine diphosphate-induced platelet aggregation.

the need to continue preoperative treatments, including antiplatelet agents intraoperatively and postoperatively in most vascular surgery settings.<sup>19</sup> None of the studies in which platelet-inhibitor treatments were continued report a clinical increased rate of bleeding. The benefit largely overcomes the risk.

Surgery, especially vascular surgery, seems to enhance the existence of an hypercoagulable state. One can legitimately wonder whether such an antiplatelet treatment should be interrupted as it is still commonly observed in many vascular patients. In elective orthopedic surgery, a recent study showed the benefit of a continuous nonsteroidal antiinflammatory agent infusion in reducing the incidence of postoperative ischemia.<sup>20</sup> The purpose of this study was to control pain, but it can be suggested that the potent antiplatelet effect of the drug could also explain the decreased postoperative ischemia. In our limited series of patients, no antiplatelet treatment was given before, during, and after the procedure, and no particular thrombotic clinical event was observed. Furthermore, troponin Ic levels did not increase postoperatively (data not shown). However, the small number of patients included in this biologic study do not allow us to draw any conclusion regarding the relation between cardiac ischemia or thrombotic episodes and platelet activation.

If the postoperative increase of fibrinogen rate has

already been reported by other investigators after aortic surgery,<sup>1</sup> until now, T-AT level had never been evaluated in this setting. It could be hypothesized that the lack of increase of such a thrombin generation marker is related to the constant use of intravenous unfractionated heparin immediately before aortic cross-clamp and of low molecular-weight heparin (nadroparin) postoperatively (subcutaneous injection) for venous thrombosis prophylaxis. Conversely, the intraoperative decrease in T-AT values could be caused by heparin injection.

We observed a postoperative increase in PAI-1 levels. This temporary increase of the natural inhibitor of tissue plasminogen activator may be responsible for an impairment of the naturally occurring fibrinolysis and an increase in the risk of myocardial ischemia.<sup>21</sup> Killewich *et al.*<sup>22</sup> showed that a defective endogenous fibrinolytic activity occurs in the early postoperative period after infra-inguinal reconstruction. The tissue plasminogen activity decreased temporarily after the procedure. Higher PAI-1 levels were observed postoperatively and remained elevated through the second day. The fibrinolytic shutdown with a return to baseline values was obtained 72 h after surgery. Rosenfeld *et al.*<sup>3</sup> observed an immediate postoperative (+ 24 h) increase in PAI-1 levels in patients undergoing lower-extremity vascular reconstruction. Furthermore, basal and postoperative PAI-1 values were higher in the group of patients devel-

**Table 3. Coagulation and Fibrinolysis**

	T1	T2	T3	T4	T5	T6
PT (%)	100.5 ± 7.3	67.7 ± 15.9	88.5 ± 15.9	88.9 ± 10.1	90.6 ± 15	96.1 ± 7.5
APTT (s)	28.4 ± 4.5	> 180	31.2 ± 9.6	35.2 ± 9.6	38.8 ± 15.4	31.8 ± 5.6
TT (s)	17.4 ± 3.0	> 120	18.2 ± 7.1	19.3 ± 18.1	21.2 ± 14.7	ND
Fibrinogen (g/l)	3.2 ± 0.6	2.2 ± 0.6	2.0 ± 0.7*	3.4 ± 0.7	5.2 ± 1.1*	5.9 ± 1.0*
T-AT (μg/l)	19.1 ± 18.3	7.9 ± 4.7*	15.5 ± 10.3	14.1 ± 12.1	11.9 ± 8.6	ND
PAI-1 (ng/ml)	8.9 ± 6.4	3.3 ± 3.1	22.8 ± 12.4*	16.4 ± 13.0*	7.31 ± 5.26	ND

Patients were administered heparin at T2. Values are expressed as mean ± SD. Six points of measurements were defined: before induction (T1), 1 h after incision (T2), 1 h after extubation (T3), 24 h postoperatively (T4), 48 h postoperatively (T5), and at day 7 (T6). No measurements were performed at T6 for thrombin time (TT), thrombin-antithrombin complexes (T-AT), and plasminogen activator inhibitor 1 (PAI-1).

\* *P* < 0.05 versus T1.

PT = prothrombin time; APTT = activated partial thromboplastin time; ND = not determined.

opening a bypass thrombosis. A return to PAI-1 baseline rate was observed at day 3. Conversely, an increase of fibrinogen plasma level was recorded at day 3 (+ 72 h). Our data are in accordance with all of these findings.

In conclusion, this study has mainly evidenced that platelets were more easily activated during the early postoperative period. The association of this phenomenon with an increased fibrinogen rate and a temporary shut down of the fibrinolysis process may indicate an increased thrombotic risk in patients undergoing major vascular surgery. The potential occurrence of an ischemic event should be considered in such a surgical context, which has led to the proposal of a study to evaluate the benefit/risk ratio of antiplatelet and anticoagulant agents in this setting.

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