Activation of Coagulation and Fibrinolysis during Coronary Surgery

On-pump versus *Off-pump Techniques*

Valter Casati, M.D.,* Chiara Gerli, M.D.,† Annalisa Franco, M.D.,† Patrizia Della Valle, B.S.,‡ Stefano Benussi, M.D.,§ Ottavio Alfieri, M.D.,‖ Giorgio Torri, M.D.,# Armando D'Angelo, M.D.**

Background: **The authors studied the changes in selected hemostatic variables in patients undergoing coronary surgery with on-pump coronary artery bypass grafting (CABG) or off-pump coronary artery bypass surgery (OPCAB) techniques.**

Methods: **Platelet counts and plasma concentrations of antithrombin, fibrinogen, D dimer, α_2 antiplasmin, and plasminogen were measured preoperatively, 5 min after administration of heparin, 10 min after arrival in the intensive care unit, and 24 h after surgery in patients scheduled to undergo OPCAB (n = 15) or CABG (n = 15). To correct for dilution, hemostatic variables and platelet counts were adjusted for the changes in immunoglobulin G plasma concentrations and hematocrit, respectively.**

Results: **Adjusting for dilution, antithrombin and fibrinogen concentrations decreased to a similar extent in patients undergoing OPCAB or CABG (pooled means and 95% confidence limits of the mean: 95.5% of baseline, 93–98%, P = 0.002, and 91.7% of baseline, 88–95%, P = 0.0001), respectively, whereas α_2-antiplasmin concentrations were unchanged. Only CABG was associated with a reduction in platelet counts (76% of baseline, 66–85%, P = 0.0001), plasminogen concentrations (96% of baseline, 91–99%, P = 0.011), and increased D-dimer formation (476%, 309–741%, P = 0.004). Twenty-four hours after surgery, platelet counts were still lower in patients undergoing CABG (P = 0.049), but all the investigated variables adjusted for dilution were similar in the two groups.**

Conclusions: **Coronary surgery causes a net consumption of antithrombin and fibrinogen. A transient decrease in platelet counts, with plasminogen activation and increased D-dimer formation, however, is only observed with CABG. Twenty-four hours after surgery, the hemostatic profiles of patients in both groups are similar.**

DESPITE efforts to improve the biocompatibility of the circuits for extracorporeal circulation, activation of inflammatory pathways of coagulation and fibrinolysis remains of major concern for the potential pathologic consequences. The inflammatory response to cardiopulmonary bypass (CPB) rarely leads to clinically relevant organ dysfunction,[1–3] but perioperative bleeding syndromes are not uncommon complications of CPB.[4] The resulting increased need for transfusion therapy and for surgical reexploration may result in increased morbidity and mortality.[5,6]

Beating-heart coronary surgery without the use of CPB was proposed long ago. Kolessov[7] used this technique in the 1960s to perform the first myocardial revascularizations with the left internal mammary artery to the left anterior descending coronary artery. However, technical difficulties in performing adequate anastomoses, particularly in the territory of the circumflex coronary artery, resulted in abandonment of this technique and greater use of CPB. Recently, through the introduction of better techniques and stabilizing systems, off-pump coronary artery bypass surgery (OPCAB) has gained in popularity.[8–10] One of the proven advantages of avoiding CPB in coronary surgery is a significant reduction of perioperative bleeding.[11] OPCAB may affect hemostatic competence to a lesser degree than coronary artery bypass grafting with CPB (CABG) does, but no study has directly compared hemostatic variables in patients undergoing coronary surgery with the two techniques. The aim of the current study was to compare the changes in selected coagulation and fibrinolysis variables in patients undergoing CABG or OPCAB.

Methods

After institutional review board approval (Ethical Committee, San Raffaele Hospital, Milan, Italy), 15 patients scheduled to undergo elective coronary surgery with CPB and 15 patients scheduled to undergo beating-heart coronary surgery, enrolled from November 1998 to January 1999, were prospectively studied after informed consent was obtained. The choice of surgical technique was established with predetermined criteria. Indications for OPCAB were as follows: (1) single-vessel disease involving the anterior descending coronary artery, without the possibility to have a catheter-based intervention; (2) restenosis after angioplasty or stent placement; and (3) multivessel coronary disease in patients for whom CPB was contraindicated because of associated comorbid conditions (severe chronic obstructive pulmonary disease, chronic renal insufficiency on dialysis, cerebrovascular diseases, severe peripheral vascular disease). For homogeneity purposes, patients were included in

* Consultant Anesthesiologist, Department of Anesthesiology, Division of Cardiac Anesthesia and Intensive Care, † Fellow, Department of Anesthesiology, ‡ Investigator, ** Head, Coagulation Service and Thrombosis Research Unit, § Consultant Surgeon, ‖ Head, Division of Cardiac Surgery, # Professor of Anesthesiology, University of Milan, and Head, Department of Anesthesiology.

Address reprint requests to Dr. Casati: Division of Cardiac Anesthesia and Intensive Care, Policlinico di Monza, via Amati 111, 20052, Monza (Milano), Italy. Address electronic mail to: valter.casati@tin.it. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

the CABG group only if three or fewer distal anastomoses were to be performed. Preoperative exclusion criteria from the study were history of hematologic disorders and liver disease (active chronic hepatitis, cirrhosis). Patients were enrolled in the study irrespective of preoperative treatment with aspirin or heparin.

Surgical Protocol

All patients were premedicated with intramuscular scopolamine (0.5 mg), intramuscular morphine (0.1 mg/kg), and oral diazepam (0.1 mg/kg). Anesthesia was induced with fentanyl (0.02 mg/kg) and propofol (2 mg/kg) or midazolam (0.15 mg/kg) in patients with reduced cardiac function, defined as left ventricular ejection fraction below 35%; muscle relaxation was obtained with pancuronium bromide (0.1 mg/kg). Anesthesia was maintained with fentanyl (up to 0.05 mg/kg), an infusion of propofol $(6-10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1})$, or midazolam $(0.1-0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1})$ in patients with reduced left ventricular ejection fraction, and isoflurane and pancuronium as needed. All patients underwent surgery through a full median sternotomy. The left internal thoracic artery was harvested in each patient with a conventional pleurotomy access; if necessary, a tract of saphenous vein was also isolated. No patient had isovolemic hemodilution or received perioperative antifibrinolytic drugs.

CABG Technique. Before aortic cannulation, porcine mucous heparin (3 mg/kg) was administered to obtain, during CPB, a celite-activated coagulation time (ACT) (Hemocron 8000, International Technidyne Corp., Edison, NJ) greater than 480 s. The circuit for CPB included a centrifugal pump, warranting a nonpulsatile blood flow, and a hollow fiber membrane oxygenator (Compact Flow D 708; Dideco, Mirandola, Italy). Blood temperature was kept between 32–35°C. Myocardial protection during aortic cross-clamping was achieved with the Buckberg method of blood cardioplegia.[12] At the end of CPB, heparin was antagonized with protamine sulphate (1:1 ratio); further doses of 50 mg were eventually administered to obtain an ACT equal or shorter than baseline. The remaining blood in the circuit and blood loss aspired by the surgical field were concentrated with a cell separator (Compact Advanced; Dideco) and reinfused.

OPCAB Technique. After opening the pericardium, a heparin dose of 1 mg/kg was administered, and an ACT greater than 250 s was maintained with supplemental doses of 50 mg until completion of the anastomoses. A stabilizer system (Octopus System; Medtronic Inc., Minneapolis, MN) was positioned in the sternal wound. No drugs were administered to decrease heart frequency. Coronary arteries were occluded, proximally and distally, by a 4-0 polytetrafluoroethylene suture passed through a silicone tube to avoid direct contact between the suture and the vessel wall. After completion of revascularization, the heparin effect was reversed with

protamine sulphate (ratio 1:1), and further doses of 50 mg were administered, when needed, to obtain an ACT equal to or shorter than baseline. Only in the case of significant intraoperative bleeding, a cell separator was used to concentrate the blood loss, and this blood was reinfused. Requirement for intraoperative and postoperative allogeneic transfusions and the amount of postoperative bleeding in the first 24 h after surgery were recorded in all patients.

Blood Sampling and Processing

Venous samples were obtained through the heparinized distal line of the central venous catheter and were collected in siliconized Vacutainer tubes (Becton Dickinson, Plymouth, United Kingdom) after induction of anesthesia (time 1), 5 min after administration of heparin (time 2), 10 min after arrival in the intensive care unit (time 3), and 24 h after the end of surgery (time 4). All samples were obtained with a two-syringe technique: 10 ml blood was aspired in the first syringe and discarded. Blood obtained with the second syringe was dispensed in test tubes containing 5.4 mg K_2-ethylenediaminetetracetic acid (3.0 ml) or 3.8% sodium citrate (1:9, vol:vol; 3.6 ml). Within 1 h after blood collection, citrated platelet-poor plasma was obtained by centrifugation for 20 min at 2,000g at room temperature.

Prothrombin time and activated partial thromboplastin time were measured from fresh plasma samples. Aliquots of platelet-poor plasma (0.5 ml) were snap-frozen and stored at −80°C until assay.

Assay Methods

Hematocrit, hemoglobin, and platelet counts were measured with an automated analyzer (HST 402; Sismex Corporation, Kobe, Japan). All determinations of hemostatic variables were performed with a fully automated coagulometer (STA; Diagnostica Stago, Asnier sur Seine, France). Reagents for activated partial thromboplastin time (STA APTT Kaolin), fibrinogen (clotting assay, STA Fibrinogen), antithrombin (amidolytic activity, STA Antithrombin III), α_2-antiplasmin (amidolytic activity, STA Antiplasmin), and quantitative D-dimer determinations (immunoturbidimetric assay, STA Liatest D-DI), were obtained from Roche Diagnostic (Mannheim, Germany).

Prothrombin times were measured with Hemoliance Recombiplastin IL (Instrumentation Laboratory, Lexington, MA), and plasminogen concentrations (amidolytic activity) were measured with the Coamatic kit (substrate S-2403; Chromogenix AB, Mölndal, Sweden). Activated partial thromboplastin time and prothrombin time results were expressed as ratios using as denominators the activated partial thromboplastin times and prothrombin times measured in normal pooled plasma obtained from 40 healthy volunteers. The same normal pooled plasma—arbitrarily given a value of 100%—was used to construct calibration curves for all the amidolytic assays.

Plasma immunoglobulin (Ig) G concentrations were measured by immunonephelometry (Tina-Quant IgG Kit; Boehringer, Mannheim, Germany) in a Modular Hitachi 917 (Roche Diagnostic).

Statistical Methods

Normality of the distribution of continuous variables was tested by the Shapiro-Wilks test. Means ($\pm$ SDs, 95% confidence limits of the mean, or both) or medians (and interquartile ranges) for non–normally distributed continuous variables were compared by the Student t test (two-tailed) or the Mann–Whitney U test, respectively. Discrete variables were analyzed with the chi-square test or the Fisher exact test as appropriate.

The changes in laboratory variables for patients undergoing the two modalities of surgery between times 1 and 2, times 2 and 3, times 3 and 4, and times 1 and 4 were tested by two-way analysis of variance. D-dimer values were log-transformed to obtain normal distributions. The analysis was conducted for both unadjusted data and for data adjusted for dilution, with the latter data expressed as percent variations over time 1. Hemostatic variables were adjusted for dilution using the correction factor $[IgG]_{initial} - [IgG]_{timepoint}/[IgG]_{initial}$. Platelet counts were adjusted using the correction factor $[\text{Platelet count}]_{initial} - [\text{Platelet count}]_{timepoint}/[\text{Platelet count}]_{initial}$. Post hoc comparisons were performed with the Student t test for paired or nonpaired data (two-tailed) and applying the Bonferroni correction. Dependency of the changes in laboratory variables (adjusted for dilution) at time 3 on the total surgical time was analyzed by least-square linear regression. All analysis was performed with the SPSS 6.0 statistical package (SPSS Inc., Chicago, IL).

Results

The two groups of patients undergoing either CABG or OPCAB were homogeneous for demographic and clinical characteristics at baseline (table 1). As expected, the two modalities of surgery differed for the doses of heparin and protamine administered, CPB time, aortic cross-clamping time, and total surgical time (table 2). Postoperative bleeding and the amount of perioperative allogeneic transfusions were similar in the two groups of patients (table 2).

Surgery-dependent Changes in Laboratory Variables

After induction of anesthesia (time 1), the investigated laboratory variables were all similar in the two groups of patients ($P \geq 0.16$) (table 3).

At time 2, hemoglobin, hematocrit, platelet counts, and D-dimer concentrations were unchanged in both groups of patients ($P \geq 0.08$). Prothrombin time ratios were increased in both groups of patients ($P = 0.0001$), and because of the higher doses of heparin administered,

Table 1. Baseline Characteristics

Variable	OPCAB Group (N = 15)	CABG Group (N = 15)	P*
Age (yr)	61 $\pm$ 10	59 $\pm$ 9	0.6
Sex, N (%) male	13 (87)	13 (87)	1
Height (cm)	167 $\pm$ 7	171 $\pm$ 6	0.09
Weight (kg)	73 $\pm$ 9	74 $\pm$ 8	0.6
Baseline ejection fraction (%)	45 $\pm$ 15	53 $\pm$ 12	0.1
Previous AMI, N (%)	7 (47)	5 (33)	0.4
Coexisting illness, N (%)			
Hypertension	8 (53)	8 (53)	1
Diabetes	4 (27)	3 (20)	0.5
Peripheral vascular disease	1 (7)	3 (20)	0.3
COPD	4 (27)	3 (20)	0.5
Preoperative aspirin, N (%)	6 (40)	5 (33)	0.7
Preoperative heparin, N (%)	3 (20)	3 (20)	1

Plus-minus values are mean $\pm$ SD.

* t test, chi-square test, or Fisher exact test as appropriate; significance for $P < 0.05$.

AMI = acute myocardial infarction; CABG = on-pump coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; OPCAB = off-pump artery bypass grafting.

patients undergoing CABG had greater prothrombin time ratios than patients undergoing OPCAB did ($P = 0.0001$). Activated partial thromboplastin time determinations were not performed because of the much higher sensitivity to heparin of the assay. All the remaining variables decreased significantly and to a similar extent in both groups of patients ($P \leq 0.004$).

Between times 2 and 3, all the laboratory variables showed a significant decrease in both groups of patients ($P \leq 0.001$), with the exception of D-dimer concentrations. At time 3, hematocrits ($P = 0.013$), platelet counts ($P = 0.0001$), and fibrinogen concentrations ($P = 0.013$) were lower in CABG patients than in OPCAB patients. In addition, two-way analysis of variance showed significant interactions between time and the modality of surgery for hemoglobin ($P = 0.023$), prothrombin time ($P = 0.0001$), antithrombin ($P = 0.008$), and plasminogen concentrations ($P = 0.004$), but post hoc analysis did not reach statistical significance in the comparison of the two groups of patients. Between times 2 and 3, D-dimer concentrations increased significantly only in CABG patients ($P = 0.0001$), and they were higher at time 3 in CABG patients than in OPCAB patients ($P = 0.005$).

Between times 3 and 4, significant increases in fibrinogen ($P = 0.0001$) and α_2-antiplasmin concentrations ($P = 0.0001$) were observed in both groups of patients. At time 4, hemoglobin ($P = 0.02$), hematocrit ($P = 0.01$), and platelet counts ($P = 0.049$) were significantly lower in CABG than in OPCAB patients, while all the remaining hemostatic variables considered were similar in the two groups of patients. In both groups, fibrinogen ($P = 0.0001$) and α_2-antiplasmin concentrations ($P = 0.04$) were higher at time 4 than at time 1.

Plasma IgG concentrations, not reported to be influenced by surgery in the short term, were measured as a

Table 2. Operative Data, Allogeneic Transfusions, and Postoperative Bleeding

Variable	OPCAB Group (N = 15)	CABG Group (N = 15)	P*
REDO, N (%)	1 (7)	3 (20)	0.3
CPB time (min)	0	67 [36–141]	< 0.0001
ACC time (min)	0	54 [27–111]	< 0.0001
Closure time (min)	30 [20–50]	45 [30–120]	0.001
Surgical time (min)	165 [98–240]	200 [135–505]	0.02
Distal anastomoses (N)	2 [1–3]	2 [1–3]	0.1
Total heparin dose (mg)	80 [50–150]	240 [210–400]	0.0001
Total protamine dose (mg)	80 [50–150]	250 [200–400]	0.0001
IABP, N (%)	1 (7)	1 (7)	1
PRBC OR, units (patients transfused)	0	5 (1)	0.5
Total PRBC, units (patients transfused)	11 (4)	18 (5)	0.5
FFP OR, units (patients transfused)	0	0	1
Total FFP, units (patients transfused)	10 (2)	14 (3)	0.1
PLTC OR, units (patients transfused)	0	0	1
Total PLTC, units (patients transfused)	0	8 (1)	0.5
Total bleeding (ml/24 h) per patient	750 [500–900]	850 [500–1450]	0.41

Normally distributed data are expressed as mean ± standard deviation; non–normally distributed data are indicated as median [25–75 percentiles]. Closure time is measured from protamine administration until the end of surgical procedures. t test, chi-square test, or Mann–Whitney U test as appropriate; significance for $P < 0.05$.

ACC = aortic cross-clamping; CABG = on-pump coronary artery bypass grafting; CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; IABP = intraaortic balloon pump; OPCAB = off-pump artery bypass grafting; OR = operating room; PLTC = platelet concentrate; PRBC = packed red blood cells.

marker of the degree of plasma dilution occurring with the two surgical modalities, of blood loss, and of the exchange of plasma proteins with the extravascular spaces. At time 2, IgG concentrations were significantly reduced with respect to time 1 ($P = 0.0001$), and they were similar in the two groups of patients. Between times 2 and 3, a further decrease in IgG concentrations was observed ($P \leq 0.002$), which was greater in CABG patients than in OPCAB patients ($P = 0.006$). At time 4, IgG concentrations were similar in the two groups of patients, and they were lower than those recorded at time 3 ($P = 0.021$) and at time 1 ($P = 0.0001$).

Surgery-dependent Changes in Laboratory Variables Adjusted for Dilution

Percent variations over time 1 in platelet counts, adjusted at times 2, 3, and 4 for the changes in hematocrit

and in hemostatic variables and adjusted at times 2, 3, and 4 for the changes in IgG concentrations are shown in table 4.

At time 2, all the adjusted variables did not show changes over time 1 and were similar in the two groups of patients.

At time 3, a significant decrease in antithrombin (pooled mean: 95.5% of baseline; 95% confidence limits of the mean: 93–98%, $P = 0.002$) and fibrinogen concentrations (pooled mean: 91.7% of baseline; 88–95%, $P = 0.001$) was observed at time 3. At this time, a reduction in platelet counts was only observed after CABG ($P = 0.0001$), with platelet counts 24% lower in CABG than in OPCAB patients ($P = 0.001$). A fivefold increase in D-dimer concentrations, reflecting fibrin formation and degradation, was only observed after CABG ($P = 0.0001$), with percent variations in D-dimer con-

Table 3. Changes in Laboratory Variables in Patients Who Underwent the Two Methods of Surgery

Variable	Time 1 OPCAB	Time 1 CABG	Time 2 OPCAB	Time 2 CABG	Time 3 OPCAB	Time 3 CABG	Time 4 OPCAB	Time 4 CABG
Hemoglobin (g/dl)	14.7 ± 1.5	14.7 ± 0.7	13.8 ± 1.4	13.9 ± 1.1	12.6 ± 1.4	11.4 ± 1.5	12.3 ± 1.5	11.1 ± 1.0
Hematocrit (%)	43.5 ± 3.5	43.7 ± 1.8	41.4 ± 3.2	41.7 ± 2.2	38.3 ± 3.8	34.1 ± 4.3	36.9 ± 4.3	33.2 ± 2.7
Platelet count (10^3/mm^3)	208 ± 49	202 ± 47	215 ± 45	207 ± 48	177 ± 40	112 ± 36	179 ± 43	137 ± 68
PT (ratio)	1.16 ± 0.22	1.10 ± 0.07	2.24 ± 1.51	8.87 ± 3.30	1.22 ± 0.10	1.23 ± 0.12	1.14 ± 0.10	1.18 ± 0.15
APTT (ratio)	1.03 ± 0.19	1.03 ± 0.15	—	—	1.27 ± 0.60	1.06 ± 0.13	0.99 ± 0.11	1.17 ± 0.37
Antithrombin (%)	86 ± 14	83 ± 6	75 ± 12	78 ± 13	68 ± 10	62 ± 12	72 ± 9	65 ± 13
Fibrinogen (mg/dl)	360 ± 61	324 ± 75	311 ± 65	287 ± 62	292 ± 54	231 ± 63	424 ± 69	373 ± 67
D dimer (mg/l)	0.50 (0.30–1.78)	0.51 (0.39–0.79)	0.40 (0.18–0.50)	0.48 (0.32–0.89)	0.61 (0.46–1.06)	1.94 (1.53–2.43)	0.81 (0.62–2.38)	1.02 (0.63–1.50)
Plasminogen (%)	102 ± 15	98 ± 12	89 ± 12	91 ± 18	85 ± 10	72 ± 16	82 ± 16	74 ± 20
α_2 Antiplasmin (%)	92 ± 10	89 ± 10	77 ± 10	81 ± 15	74 ± 10	65 ± 10	89 ± 10	79 ± 20
IgG (g/l)	8.1 ± 2.6	7.3 ± 1.3	6.8 ± 1.3	6.5 ± 1.3	6.4 ± 1.4	5.0 ± 1.2	5.9 ± 1.6	4.7 ± 0.9

All variables are expressed as mean ± SD except D-dimer concentrations, which are reported as median and interquartile range.

Time 1 = after the induction of anesthesia; time 2 = 5 min after the administration of heparin; time 3 = 10 min after arrival in intensive care unit; CABG = coronary artery bypass graft; OPCAB = off-pump artery bypass graft.

Table 4. Percent Variations over Time 1 of Platelet Counts and Hemostatic Variables Adjusted for Dilution

Variable	Time 2		Time 3		Time 4	
	OPCAB	CABG	OPCAB	CABG	OPCAB	CABG
Platelet count (10^3/mm^3)	102 (93–112)	107 (95–118)	100 (91–108)	76 (66–85)	105 (93–116)	92 (69–114)
Antithrombin (%)	99 (95–102)	103 (99–107)	96 (93–99)	96 (91–100)	101 (96–106)	105 (98–111)
Fibrinogen (mg/dL)	97 (93–101)	99 (92–106)	95 (91–98)	89 (82–95)	149 (132–167)	159 (141–177)
D dimer (mg/L)	69 (41–115)	129 (72–233)	104 (75–144)	476 (309–741)*	353 (227–548)	260 (179–377)
Plasminogen (%)	100 (94–105)	101 (96–105)	103 (99–107)	96 (91–100)	101 (91–111)	100 (91–110)
α_2 Antiplasmin (%)	95 (90–99)	96 (92–100)	100 (94–106)	96 (88–103)	119 (110–127)	120 (106–134)

All variables are expressed as mean and 95% confidence limits of the mean. Time 2 = 5 min after the administration of heparin; time 3 = 10 min after arrival in intensive care unit; time 4 = 24 h after the end of surgery. Platelet counts at times 2, 3, and 4 are adjusted for the changes in hematocrit concentration; the remaining variables are adjusted at times 2, 3, and 4 for the changes in plasma IgG concentrations.

* $P = 0.001$.

CABG = coronary artery bypass graft; IgG = immunoglobulin G; OPCAB = off-pump artery bypass graft.

centrations significantly greater in CABG than in OPCAB patients at time 3 ($P = 0.001$). Accordingly, plasminogen concentrations showed a moderate but significant decrease only in CABG patients ($P = 0.011$). At time 3, α_2-antiplasmin concentrations were unchanged after either modality of surgery. No significant relation was observed between the changes in any of the laboratory variables evaluated and the total surgical time.

Between times 3 and 4, similar increases in the plasma concentrations of antithrombin ($P = 0.001$), fibrinogen ($P = 0.0001$), and α_2 antiplasmin ($P = 0.0001$) were observed in the two groups of patients, with fibrinogen and α_2-antiplasmin concentrations 54.5% (pooled mean: 42.8–66.3%, $P = 0.0001$) and 19.2% (pooled mean: 11.4–27.2%, $P = 0.0001$) higher than at time 1. Platelet counts increased only in CABG patients ($P = 0.027$). Percent variations in D-dimer concentrations were similar at time 4 in the two groups of patients, resulting from an increase in D-dimer concentrations in OPCAB patients ($P = 0.015$) and a decrease in D-dimer concentrations in CABG patients ($P = 0.002$). At time 4, plasminogen concentrations were unchanged over time 3 in both groups of patients.

Discussion

The abnormalities of coagulation and fibrinolysis variables associated with CPB heart surgery have been extensively investigated because of the occurrence of hemorrhagic perioperative syndromes, which significantly complicates the outcome of heart surgery patients.[13] Recently, OPCAB has been revisited because of the introduction of stabilizer systems permitting satisfactory results,[14,15] and an increasing number of centers have adopted this modality of surgery as their first choice.[8–10,16]

This study is the first investigation directly comparing selected coagulation and fibrinolysis variables in CABG and OPCAB patients free of perioperative and postoperative complications. Because of the obvious difference in

the degree of hemodilution occurring with the two surgical modalities, we chose to adjust the changes in hemostatic variables for those observed in total IgG concentrations. IgG concentrations have not been reported to be affected by surgery in the short term. They are not involved in metabolic pathways potentially altered by trauma, and, differently from erythrocytes, their plasma concentrations may account for the exchange of plasma proteins between intravascular and extravascular compartments. Our results show that after correction for this variable, fibrinogen, antithrombin, and α_2-antiplasmin concentrations were not different in patients undergoing CABG or OPCAB and that both modalities of surgery involved a significant net consumption of antithrombin and fibrinogen. These findings are not surprising when considering the threefold higher dose of heparin infused in CABG patients (table 2) and considering that thrombin generation during CPB does not result from exposure of blood to foreign surfaces (contact activation) but is triggered by the tissue factor–factor VIIa pathway, possibly in response to the cutting of blood vessels.[17,18] Earlier studies on CBP surgery reported conflicting results, with the additional bias represented by priming of the extracorporeal circuit with either blood or saline. Mammen et al.[19] found that the decreases in fibrinogen, antithrombin, plasminogen, and α_2-antiplasmin concentrations were consistent with the decrease in hematocrit. Plasminogen and antithrombin, but not α_2 antiplasmin, were found to decrease much more than dilution in another study.[20] In contrast, Konsgaard et al.[21] observed a decrease in α_2 antiplasmin, but not in plasminogen and antithrombin, when correcting for the hemoglobin concentration.

Significant changes in platelet counts, D-dimer concentrations, and plasminogen concentrations were only associated with cardiopulmonary bypass surgery (tables 3 and 4). When adjusted for the hematocrit, platelet counts were 24% lower than baseline in patients undergoing CABG. The changes in platelet number and function during CPB and their relation with perioperative

hemorrhagic syndromes have been extensively studied.[20,22–26] Plasma D-dimer concentrations were not significantly increased after surgery in OPCAB patients, but they were approximately fivefold higher in CABG patients. A 4% decrease in plasminogen concentrations was only observed after CABG surgery. These findings are consistent with increased plasminogen activation during CPB. Activation of fibrinolysis in CPB surgery has been reported in many studies, with both the intrinsic (factor XIIa- and kallikrein-dependent) and extrinsic (tissue plasminogen activator–dependent) mechanisms of plasminogen activation being involved.[21,27–31] Increased D-dimer concentrations after CPB surgery have been consistently reported, with the exception of one study in which a poorly sensitive assay was adopted.[32] Two studies have compared the changes in D-dimer concentrations in patients undergoing cardiac surgery with CPB and patients undergoing thoracic noncardiac surgery.[31,33] Both studies observed a significant increase in D-dimer concentrations after surgery only in CABG patients. Accordingly, Mariani *et al.*[34] did not observe significantly increased D-dimer concentrations during surgery in a group of 22 patients undergoing beating-heart coronary surgery. Differently from patients undergoing thoracic noncardiac surgery, OPCAB patients are infused with a substantial amount of heparin. Heparin injection was reported to increase circulating plasmin activity[21,26] and D-dimer concentrations[26] before institution of cardiopulmonary bypass. In this study, we did not observe a significant increase in D-dimer concentrations after heparin injection (time 2; tables 3 and 4).

Twenty-four hours after surgery, platelet counts were still significantly lower in CABG than in OBCAB patients, but the hemostatic variables evaluated were all similar in the two groups of patients. When accounting for dilution, there was no difference at this time in any of the laboratory variables investigated between the two groups of patients. With respect to postoperative concentrations, a significant increase in antithrombin concentrations was observed for both groups of patients, and platelet counts increased by approximately 20% in patients undergoing CABG. The acute phase reactant fibrinogen and α_2 antiplasmin increased to a much greater extent over preoperative concentrations, as previously reported.[19,30,32] These data suggest a similar pattern of postoperative consumption, production, or both of the plasma proteins investigated after either modality of surgery. D-dimer concentrations showed a different pattern of changes after OPCAB and CABG surgery, possibly reflecting a different time course in activation of fibrinolysis. They decreased by more than 50% in patients undergoing CABG, whereas they increased by more than 2.5-fold in patients undergoing OPCAB. This finding is in accordance with the transient increase in the fibrinolytic activity of patients undergoing CPB surgery[27–29] and with previous reports showing a postoperative increase in D-dimer concentrations in patients undergoing both thoracic noncardiac surgery[31,33] and beating-heart revascularization surgery.[34] As previously suggested, increased D-dimer concentrations 24 h after surgery may be the evidence of clot formation at sites of surgical injuries and do not necessarily reflect coagulopathy[32] or hypercoagulability.

In conclusion, uncomplicated heart revascularization surgery involves a net consumption of antithrombin and fibrinogen. However, transient platelet consumption, plasminogen activation, and D-dimer formation are only observed with on-pump coronary surgery. Twenty-four hours after surgery, the hemostatic patterns of patients undergoing CABG and OPCAB are similar.

References

1. Hsu Li-Chien: Biocompatibility in cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1997; 11:376–82

2. Butler J, Rocker GM, Westaby S: Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 1993; 55:552–9

3. Asimakopoulos G, Smith PLC, Ratnatunga CP, Taylor KM: Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. Ann Thorac Surg 1999; 68:1107–15

4. Bracey AW, Radovancevic R: The hematologic effects of cardiopulmonary bypass and the use of hemotherapy in coronary artery bypass grafting. Arch Pathol Lab Med 1993; 118:411–6

5. Williamson LM, Lowe S, Love EM, Cohen H, Soldan K, McClelland DBL, Skacel P, Barbara JAJ: Serious hazards of transfusion (SHOT) initiative: Analysis of the first two annual reports. Br Med J 1999; 319:16–9

6. Moulton MJ, Creswell LL, Mackey ME, Cox JL, Rosembloom M: Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. J Thorac Cardiovasc Surg 1996; 111:1037–46

7. Kolessov VI: Mammary artery-coronary artery anastomosis as a method of treatment for angina pectoris. J Thorac Cardiovasc Surg 1967; 54:534–44

8. Cartier R: Systematic off-pump coronary artery revascularization: experience of 275 cases. Ann Thorac Surg 1999; 68:1494–7

9. Koutlas TC, Elbeery JR, Williams JM, Moran JF, Francalancia NA, Chitwood WR Jr: Myocardial revascularization in the elderly using beating heart coronary artery bypass surgery. Ann Thorac Surg 2000; 69:1042–7

10. Calafiore AM, Di Giammarco G, Teodori G, Bosco G, D'Annunzio E, Barsotti A, Maddestra N, Paloscia L, Vitolla G, Sciarra A, Fino C, Contini M: Left anterior descending coronary artery grafting via left anterior small thoracotomy without cardiopulmonary bypass. Ann Thorac Surg 1996; 61:1658–65

11. Nader ND, Khadra WZ, Reich NT, Bacon DR, Salerno TA, Panos AL: Blood product use in cardiac revascularization: Comparison of on- and off-pump techniques. Ann Thorac Surg 1999; 68:1640–3

12. Buckberg GD: Update on current techniques of myocardial protection. Ann Thorac Surg 1995; 60:805–14

13. Woodman RC, Harker LA: Bleeding complications associated with cardiopulmonary bypass. Blood 1990; 76:1680–97

14. Calafiore AM, Teodori G, Di Giammarco G, Vitolla G, Maddestra N, Paloscia L, Zimarino M, Mazzei V: Multiple arterial conduit without cardiopulmonary bypass: Early angiographic results. Ann Thorac Surg 1999; 67:450–6

15. Poirier NC, Carrier M, Lespérance J, Coté G, Pellerin M, Perrault LP, Pelletier LC: Quantitative angiographic assessment of coronary anastomoses performed without cardiopulmonary bypass. J Thorac Cardiovasc Surg 1999; 117:292–7

16. Iacò AL, Contini M, Teodori G, Di Mauro M, Di Giammarco G, Vitolla G, Iovino T, Calafiore AM: Off or on bypass: what is the safety threshold? Ann Thorac Surg 1999; 68:1486–9

17. Boisclair MD, Lane DA, Philippou H, Esnouf MP, Sheikh S, Hunt B, Smith KJ: Mechanisms of thrombin generation during surgery and cardiopulmonary bypass. Blood 1993; 82:3350–7

18. Burman JF, Chung HI, Lane DA, Philippou H, Adami A, Lincoln JCR: Role of factor XII in thrombin generation and fibrinolysis during cardiopulmonary bypass. Lancet 1994; 344:1192–3

19. Mammen EF, Koets MH, Washington BC, Wolk LW, Brown JM, Burkick M, Selik NR, Wilson RF: Hemostasis changes during cardiopulmonary bypass surgery. Semin Thromb Hemost 1985; 11:281–92

20. Holloway DS, Summariva L, Sandesara J, Vagher JP, Alexander JC, Caprini JA: Decrease platelet number and function and increased fibrinolysis contribute to postoperative bleeding in cardiopulmonary bypass patients. Thromb Haemost 1988; 59:62–7

21. Kongsgaard UE, Smith-Erichsen N, Geiran O, Bjornskau L: Changes in the coagulation and fibrinolytic systems during and after cardiopulmonary bypass surgery. Thorac Cardiovasc Surg 1988; 37:158–62

22. Harker LA, Malpass TW, Branson HE, Hessel II A, Sherrill SL: Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: Acquired transient platelet dysfunction associated with selective α-granule release. Blood 1980; 56:824–34

23. Campbell FW: The contribution of platelet dysfunction to postbypass bleeding. J Cardiothorac Vasc Anesth 1991; 5:8–12

24. Rinder CS, Bohnert J, Rinder HM, Mitchell J, Ault K, Hillman R: Platelet activation and aggregation during cardiopulmonary bypass. ANESTHESIOLOGY 1991; 75:388–93

25. Birjiniuk V, Odimet H, Pasche B, Nelson MJ, Benoit SE, Rodino LJ, Barnard M, Michelson AD: The platelet function defect of cardiopulmonary bypass. Blood 1993; 82:107–17

26. Khuri SF, Valeri CR, Loscalzo J, Weinstein MJ, Birjiniuk V, Healey NA, MacGregor H, Doursounian M, Zolkewitz MA: Heparin causes platelet dysfunction and induces fibrinolysis before cardiopulmonary bypass. Ann Thorac Surg 1995; 60:1008–14

27. Kucuk O, Kwaan HC, Frederickson J, Wade L, Green D:Increased fibrinolytic activity in patients undergoing cardiopulmonary bypass operation. Am J Hematol 1986; 23:223–9

28. Tanaka K, Takao M, Yada I, Yuasa H, Kusagawa M, Deguchi K: Alterations in coagulation and fibrinolysis associated with cardiopulmonary bypass during open heart surgery. J Cardiothorac Anesth 1989; 3:181–8

29. Paramo JA, Rifon J, Llorens R, Casares J, Paloma MJ, Rocha E: Intra- and postoperative fibrinolysis in patients undergoing cardiopulmonary bypass surgery. Haemostasis 1991; 21:58–64

30. Saatvedt K, Lindberg H, Michelsen S, Pedersen T, Geiran OR: Activation of the fibrinolytic, coagulation and plasma kallikrein-kinin systems during and after open heart surgery in children. Scand J Clin Lab Invest 1995; 55:359–67

31. Hunt BJ, Parratt RN, Segal HC, Sheikh S, Kallis P, Yacoub M: Activation of coagulation and fibrinolysis during cardiothoracic operations. Ann Thorac Surg 1998; 65:712–8

32. Comunale ME, Carr JM, Moorman RM, Robertson LK: Significance of D-dimer concentrations during and after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 1996; 10:477–81

33. Whitten CW, Greilich PE, Ivy R, Burkhardt D, Allison PM: D-dimer formation during cardiac and noncardiac thoracic surgery. Anesth Analg 1999; 88:1226–31

34. Mariani MA, Gu YJ, Boonstra PW, Grandjean JC, van Oeveren W, Ebels T: Procoagulant activity after off-pump coronary operation: is the current anticoagulation adequate? Ann Thorac Surg 1999; 67:1370–5