

# Soluble Fibrin Monomer Complex and Cardiopulmonary Bypass

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**Abstract:** Soluble fibrin monomer complexes (SFMCs) are precursors of fibrin polymer formation. Laboratory tests can be used to detect SFMCs in plasma. The purpose of this study was to determine whether a positive SFMC test is associated with pre-operative, intra-operative, and post-operative variables for patients that have undergone cardiopulmonary bypass (CPB). Pre-operative, operative, post-operative, and laboratory data from 120 consecutive adults patients (July 3, 2006 to June 29, 2007) that had undergone cardiac surgery with the use of CPB were obtained from a prospective quality control database. Two groups were created. Group 1 was all negative (NEG). This group had no SFMC test with a positive result ( $n = 60$ ) and no positive SFMCs (POS,  $n = 60$ ). Group 2 was any positive (POS).

This group had at least one positive SFMC test ( $n = 60$ ). The POS group had more patients with endocarditis (11.7% vs. 3.3%,  $p < .001$ ), chronic obstructive pulmonary disease (COPD) (18% vs. 8.3%,  $p = .005$ ), longer CPB time ( $172 \pm 64$  vs.  $151 \pm 53$  minutes,  $p = .047$ ), and fewer minimally invasive procedures (31.7% vs. 51.7%,  $p = .002$ ). The POS group required intra-operative (70.0% vs. 53.3%,  $p = .010$ ) and post-operative (75.5% vs. 45.0%,  $p < .001$ ) transfusions more frequently than the NEG group, despite similar amounts of blood loss. SFMC tests in CPB may be associated with patient pre-operative status and an increase in transfusion requirements. **Keywords:** cardiopulmonary bypass, soluble fibrin monomer complex, fibrin, coagulation, transfusion, hemostasis. *JECT. 2009;41:157–160*

Fibrin monomers (FM) are formed when thrombin cleaves one or both of the A or the B peptides of fibrinogen. In the early stages of thrombosis the FM attain stability in plasma by forming soluble FM complexes (SFMCs) with fibrinogen and fibrinogen degradation products. As the process of thrombosis continues, more FMs are created and more complexes are formed. A concentration threshold is eventually reached creating fibrin polymers that interact with factor XIII to form stable clots (1).

Because SFMCs can be detected before actual “clot” formation occurs, it has been used as a marker for imminent thrombotic events. Therefore, the test can be used to diagnose disseminated intravascular coagulation (DIC) in its early stages (2).

It is well recognized that CPB is associated with the activation of the intrinsic pathway and can result in functional platelet abnormalities, primary hypofibrinogenolysis, thrombocytopenia, heparin excess and heparin rebound,

and DIC (3–8). However, the relationships that may exist between CPB and the presence of SFMC are less well understood. Therefore, the purpose of this study was to determine whether a positive SFMC test is associated with pre-operative, intra-operative, and post-operative variables for patients that have undergone cardiopulmonary bypass (CPB).

## MATERIALS AND METHODS

### Data Collection

After institutional review board approval, data were entered into a prospective database. From July 3, 2006 to June 29, 2007 data were collected from 122 consecutive patients that have undergone cardiac surgery with the use of CPB from a single surgeon. Two patients were excluded because they were not tested for SFMCs at any time ( $n = 120$ ). Ideally, three SFMC tests were preformed: (i) pre-bypass, (ii) during bypass, and (iii) post-bypass. Not all patients had a complete series of SFMC testing.

### Anesthesia Management

Patients received 0.5–5.0 mg of midazolam in the pre-operative care unit, followed by the placement of two 16-gauge intravenous lines. After arriving in the operative suite, a radial or brachial arterial line was placed, followed

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by a continuous cardiac output pulmonary artery catheter (Edwards Lifesciences, Irvine, CA), inserted through an internal jugular introducer. Induction was accomplished by 5.0–10.0 mg midazolam, 0.5–1.0 mg fentanyl, and 7.0–10.0 mg of Pavulon (cisatracurium or vecuronium were occasionally used in lei of Pavulon to maintain a heart rate <100 bpm).

Before CPB, formal anesthesia guidelines were in place to keep fluid administration <1200 mL. Blood pressures were maintained with either Neo-Syneprine and ephedrine or epinephrine infusion through the central line. Fentanyl (as needed), Ativan (2 mg), and midazolam (5–10 mg) were given before initiation of CPB at the discretion of the anesthesia staff. In addition, 1 g of cefazolin was given <60 minutes before skin incision, followed by repeat 1-g doses every 4 hours until closure.

Amicar or aprotinin was used on all cases, with selection based on surgeon preference. If Amicar was used, 5 g was infused before CPB. If aprotinin was used, a 1-mL test dose was given, followed by 2000,000 KIU infused over 30 minutes, followed by a 100,000 KIU/h drip continued through intensive care unit (ICU) arrival.

For circulatory arrest procedures, 30 mg/kg of Solu-Medrol and 25 g of mannitol were given. During rewarming, additional fentanyl (12.5–25.0  $\mu$ g/kg) and midazolam (5.0–12.0 mg) and additional muscle relaxant were given. Before cross-clamp removal, 100 mg lidocaine and 2 g magnesium sulfate were given.

### CPB Management

The CPB circuit consisted of a an oxygenator with integrated arterial line filter and cardiotomy reservoir (Synthesis; Cobe Cardiovascular, Arvada, CO), SmART<sub>x</sub>-coated tubing (Cobe Cardiovascular), myocardial protection system (Quest Medical, Allen, TX), in-line blood gas monitoring (CDI 500; Terumo Cardiovascular, Ann Arbor, MI), and a centrifugal pump (Revolution; Cobe Cardiovascular). The circuit was primed with 1400 mL of PlasmaLyteA, 35 mEq NaHCO<sub>3</sub>, 5000 IU heparin, and 25 g mannitol. The retrograde autologous priming (RAP) technique was also used on every patient.

Autotransfusion was used with every case (CATS; Terumo Cardiovascular). A ratio of 1 part anticoagulant (30 IU heparin/mL, 0.9% NS) to 10 parts collected blood was used and was washed with a 0.9% NaCl solution on the “Quality Wash” program.

During CPB, arterial pressure was maintained between 60 and 90 mmHg, cardiac index was maintained >1.8 L/min/m<sup>2</sup>, and blood gases were managed with alpha-stat physiology ( $pH_a = 7.35$ – $7.45$ ,  $P_aCO_2 = 35$ – $45$  mmHg,  $P_aO_2 = 150$ – $250$  mmHg). Patients were cooled to a temperature of 28°C with temperature controlled according to institutional policy (gradients <6°C, maximum arterial temperature <37°C, rewarming rate <.5°C/min). Vacuum-assisted venous drainage was only used when required and never exceeded

–40 mmHg. Volume replacement during CPB was accomplished with PlasmaLyteA, with 12.5 g of albumin added per liter crystalloid solution or 5% albumin added to achieve [Albumin] >3.5 g/dL or colloid oncotic pressure (COP) >14 mmHg.

Induction of cardioplegic arrest was accomplished with 1000–1500 mL of cold (4°C) 4 blood:1 crystalloid. The Myocardial Protection System (MPS) was set to deliver 20 mEq/L KCL and 15 mEq/L of NaHCO<sub>3</sub>, with the crystalloid component consisting of 1 L .9% saline with 12.5 g mannitol. Subsequent doses were given at 15- to 20-min intervals and consisted of cold (4°C), all blood with 10–16 mEq/L KCl (adjusted to ensure electrical quiescence and avoid hyperkalemia). Antegrade cardioplegia was delivered at a system pressure of 100–150 mmHg, and retrograde cardioplegia was delivered to a coronary sinus pressure of 30–40 mmHg. Antegrade vs. retrograde delivery was based on surgeon preference and surgical procedure. Before removal of the cross-clamp, warm blood (37°C) was delivered for 5 minutes, with additional [KCl] of 8 mEq for the first minute, 4 mEq for the second minute, and 0 mEq for the remaining 3 minutes.

If Amicar was used, 5 g of Amicar was added to the pump prime, the patient was anticoagulated with a loading dose of 300 IU/kg of heparin, and additional heparin was given to during CPB to maintain an activated clotting time (ACT) > 480 seconds (ACTII; Medtronic) If aprotinin was used, 2,000,000 KIU of aprotinin was added to the pump prime, the patient was anticoagulated with 400 IU/kg of heparin, and additional heparin was given during CPB to maintain an ACT > 600 seconds. After the termination of CPB and after patient stability was assured, heparin was reversed with 0.6 mg of protamine per 100 IU heparin administered.

All patients were managed in the cardiac intensive care unit (CICU) by the surgical and nursing teams.

Tracheal extubation and discharge from the CICU were accomplished when standard clinical criteria were met. After being transferred to the surgical ward, all patient management was conducted by the surgical team. All adverse outcomes observed in the post-operative period were entered into the database by one of three physician assistants. The database was analyzed, and complications were recorded. The complications that were recorded are defined by the Society of Thoracic Surgery.

### Laboratory Test for SFMC

The SFMC test used at this hospital is the F.S. Test (Diagnostics Stago, Asnières sur Seine, France). It is a rapid qualitative slide test for SFMCs in plasma by the hemagglutination technique. The test uses human erythrocytes coated with purified fibrin monomer that agglutinate in the presence of SFMCs and is reported as either a positive or negative result. A positive test is reported when macroscopic agglutinations are readily observed after the sample

has been gently swirled for 6 minutes. The sensitivity of the F.S. Test is reported to be 94.8% in the presence of DIC and has a specificity of 96.9%.

**Group Assignments**

Two groups were created from the data analysis—group 1: all negative (NEG), this group had no SFMC test with a positive result (*n* = 60); group 2: any positive (POS): had at least one positive SFMC test (*n* = 60).

**Statistical Analysis**

Data were collected prospectively. Means and SDs were determined, *t*-tests were done, and *p* ≤ .05 was considered significant.

**RESULTS**

Group 1 (NEG) and group 2 POS both contained 60 patients that met the criteria. A group comparison is shown in Table 1. There were no significant differences between groups with respect to age, sex, left ventricular ejection fraction (LVEF), insulin dependent diabetes mellitus (IDDM), and aortic cross-clamp time. Group 2 CPB time was significantly higher than group 1 (172 ± 64 vs. 151 ± 53 minutes, *p* = .047).

Group 2 (POS) had more preoperative endocarditis compared with group 2 (NEG) (11.7% vs. 3.3%, *p* < .001). Group 2 (POS) had a higher incidence of chronic obstructive pulmonary disease (COPD) than group 1 (NEG) (18.3% vs. 8.3%, *p* = .005) and fewer minimally invasive procedures (31.7% vs. 51.7%, *p* = .002).

Group 2 (POS) required intra-operative (70.0% vs. 53.3%, *p* = .010) and post-operative (75.0% vs. 45.0%, *p* < .001) transfusions more frequently than group 1 (NEG)

**Table 1.** Patient comparison between group 1 and group 2.

Patient Data	Group 1 (NEG)	Group 2 (POS)	<i>p</i>
Age (yr)	61.6 ± 13.7	63.8 ± 14.9	NS
Sex: male (%)	60.0	66.7	
BSA (m <sup>2</sup> )	2.09 ± 0.39	2.0 ± 0.5	NS
LVEF (%)	53.1 v 9.2	49.4 ± 12.1	NS
IDDM (%)	1.7	5	NS
Endocarditis	3.3%	11.7%	<.001
COPD	8.3%	18.3%	.005
CPB time (min)	151 ± 53.2	172.7 ± 64.2	.047
Ao Xclamp (min)	114.1 ± 63.3	132.7 ± 63.3	NS

NS, not significant.

**Table 2.** Post-bypass transfusion requirements.

	Group 1 (NEG)	Group 2 (POS)	<i>p</i>
pRBC (%)	41.7	66.7	.0001
FFP (%)	23.3	45	.0001
Cryo (%)	8.3	28.8	.00001
Platelets (%)	18.3	43.3	.00001

Percent of patients receiving transfusions.

(Figure 1). After bypass, group 2 (POS) had significantly more packed red blood cells (pRBC), fresh frozen plasma (FFP), cryoprecipitate, and platelet transfusions (Table 2). Heparin and ACT management is shown in Table 3. Baseline ACT and heparin dose were the same between groups. There was significantly more heparin given during bypass in group 2 (POS). Table 3 shows complete anticoagulation data.

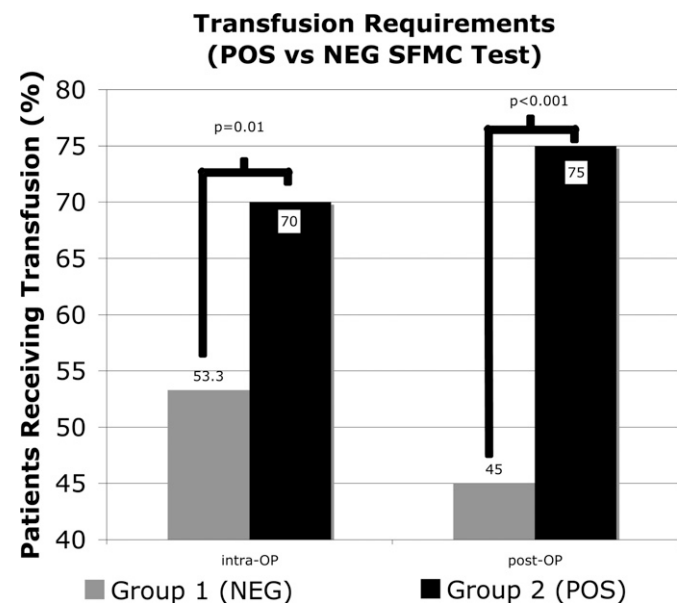
**DISCUSSION**

Thrombin cleaves fibrinopeptides from fibrinogen, forming a FM that rapidly polymerizes to form clots. Small amounts can circulate in plasma as “soluble fibrin.” Historically, testing for the presence of the soluble fibrin, SFMC, has been used as a sensitive assay to determine

**Table 3.** Anticoagulation management.

	Group 1 (NEG)	Group 2 (POS)	<i>p</i>
Baseline ACT (s)	132.2 ± 16.8	128.2 ± 17.3	NS
Heparin dose (units)	32,386.7 ± 8575.2	30,816.7 ± 7400.2	NS
Additional heparin (units)	1850.0 ± 5451.9	1100.0 ± 2304.7	NS
Pre-CPB ACT (s)	728.8 ± 206.4	705.3 ± 194.7	NS
First CPB ACT (s)	759.2 ± 192.3	711.6 ± 185.2	NS
High CPB ACT (s)	827.2 ± 154.1	791.7 ± 179.3	NS
Low CPB ACT (s)	604.1 ± 140.8	571.5 ± 154.1	NS
Last CPB ACT (s)	652.0 ± 162.9	633.1 ± 174.7	NS
Additional CPB heparin (units)	3283.3 ± 4712.4	6633.3 ± 8311.1	.008
Protamine dose (mg)	266.8 ± 60.8	247.3 ± 45.9	NS
Post-protamine ACT (s)	114.0 ± 12.5	114.1 ± 19.3	NS
Additional protamine (mg)	31.8 ± 33.5	46.3 ± 48.9	NS

NS, not significant.



**Figure 1.** Comparison of intra-operative and post-operative transfusion requirements (all blood products combined) between group 1 (NEG) and group 2 (POS) SFMC tests. Data are presented as percent of patients in group receiving a blood product transfusion.

adequacy of anticoagulation during CPB (9). More recently, elevated levels of SFMCs have been observed during sepsis (10). The possible connection between bacterial endotoxin, inflammation, and the presence of SFMCs could explain the association between patients with pre-operative endocarditis and the positive SFMC test seen in this study.

Interestingly, the presence of COPD was also statistically associated with a positive SFMC test. Perhaps, this may be indicative of arterial inflammation that may trigger coagulation and activation of complement inside the vascular system, leading to enough thrombin activity to cause a positive SFMC test.

Longer bypass time was associated with the POS group. It is thought that, during CBP, initial contact between blood and the artificial surface of the circuit induces an overall activation of the homeostatic system. Longer bypass times increase the time frame that the homeostatic system is activated and may lead to increased thrombin activity.

Transfusion requirements were statistically higher in patients who had a positive SFMC test. This may be explained by the increased consumption of coagulation factors and coagulopathy.

A limitation of this study is that the SFMC testing instructions suggest that the test is insensitive to unfractionated and low molecular weight heparins concentrations up to 2 IU/mL. This could affect the sensitivity of the test considering that all patients in this study underwent a surgical procedure with the use of CPB, and the desired procedural concentration range of heparin is 3–4 IU/mL. However, the study from which the test is based suggests heparin concentrations >12.5 NIH units/mL are needed to prolong agglutination time (11). Other limitations include the inclusion of some patients with incomplete SFMC testing, the variable sampling during CPB rather than at a specific time during CPB, and the limited number of patients sampled.

In conclusion, a positive SFMC test in patients undergoing CPB might be associated with preoperative status (COPD and endocarditis). Positive SFMC tests also seem to be associated with increased heparin and transfusion requirements. Further studies are necessary to understand the role of the SFMC test in patients undergoing CPB.

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