

The hemostatic disturbance in patients with acute aortic dissection

A prospective observational study

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Abstract

Coagulopathy is still a frequent complication in the surgical treatment of acute aortic dissection. However, the physiopathology of surgically induced coagulopathy has never been systematically and comprehensively studied in patients with acute aortic dissection. The aim of the present study was to describe the perioperative hemostatic system in patients with acute aortic dissection.

The 87 patients who underwent aortic arch surgery for acute Stanford type A aortic dissection from January 2013 to September 2015 were enrolled in this study. The perioperative biomarkers of hemostatic system were evaluated using standard laboratory tests and enzyme-linked immunosorbent assays (ELISAs) at 5 time points: anesthesia induction (T1), lowest nasopharyngeal temperature (T2), protamine reversal (T3), 4 hours after surgery (T4), and 24 hours after surgery (T5).

The ELISAs biomarkers revealed activation of coagulation (thrombin-antithrombin III complex [TAT] and prothrombin fragment 1 + 2 [F1 + 2] were elevated), suppression of anticoagulation (antithrombin III [AT III] levels were depressed), and activation of fibrinolysis (plasminogen was decreased and plasmin-antiplasmin complex [PAP] was elevated). The standard laboratory tests also demonstrated that surgery resulted in a significant reduction in platelet counts and fibrinogen concentration.

Systemic activation of coagulation and fibrinolysis, and inhibition of anticoagulation were observed during the perioperative period in patients with acute aortic dissection. Indeed, these patients exhibited consumption coagulopathy and procoagulant state perioperatively. Therefore, we believe that this remarkable disseminated intravascular coagulation (DIC)-like coagulopathy has a high risk of bleeding and may influence postoperative outcome of patients with acute aortic dissection.

Abbreviations: AAD = acute aortic dissection, AT III = antithrombin III, CPB = cardiopulmonary bypass, DIC = disseminated intravascular coagulation, ELISA = enzyme-linked immunosorbent assay, F1+2 = prothrombin fragment 1+2, FDP = fibrinogen degradation products, HCA = hypothermic circulatory arrest, INR = international normalized ratio, IQR = interquartile range, MHCA = moderate hypothermic circulatory arrest, PAP = plasmin-antiplasmin complex, SD = standard deviation, TAT = thrombin-antithrombin III complex.

Keywords: acute aortic dissection, cardiopulmonary bypass, coagulation, fibrinolysis, hypothermic circulatory arrest

1. Introduction

Acute aortic dissection (AAD) is one of the most common aortic pathological lesions and requires emergency diagnosis and

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treatment.^[1–2] Although substantial advances in surgical techniques such as selective cerebral perfusion and hypothermic circulatory arrest (HCA) have helped to improve early and long-term clinical outcomes, postoperative bleeding, and transfusion of allogeneic blood products, disseminated intravascular coagulation (DIC) and secondary surgery to manage bleeding represented some of the most common and feared complications.^[3–5] However, the physiopathology of surgically induced coagulopathy has never been systematically and comprehensively studied perioperatively in patients with AAD.

Thus, our objective in this study was to describe the status of perioperative hemostatic system in patients with AAD who underwent aortic arch surgery that involved moderate hypothermic circulatory arrest (MHCA). For this purpose, we measured biomarkers of hemostatic system using enzyme-linked immunosorbent assays (ELISA) and standard laboratory tests.

2. Methods

2.1. Patient population

From January 2013 to September 2015, a total of 87 patients with proven acute Stanford type A aortic dissection underwent a series of tests and emergent aortic arch surgery involving MHCA at our institution. All patients who received aortic arch replacements, with or without aortic valve surgery, were eligible for the study. Patients were recruited on a consecutive basis, on

the condition that they agreed to provide their informed consent. A diagnosis of AAD was confirmed by computed tomography in all patients. Exclusion criteria included the following: patients with congenital or acquired coagulation disorders, liver disease, previous surgery at the same site, death before planned surgery, stroke or myocardial infarction within 2 months before surgery, and the use of an oral anticoagulant or antiplatelet treatment within 2 to 5 days before surgery.

2.2. Study design

In this single-center prospective study, we analyzed the results of standard laboratory tests and biomarkers of hemostatic system in 87 patients with AAD who underwent aortic arch surgery. All procedures were performed by a single surgeon (XLW). The Ethics Committee at Beijing Anzhen hospital approved the study protocol (Institutional Review Board File 2014019) and consent was obtained from the patients or their relatives. The primary endpoint of this study was to evaluate the status of coagulation, anticoagulation, and fibrinolysis perioperatively in patients with AAD.

2.3. Surgical procedures

Standard anesthetic management was used with endotracheal intubation. The procedures were performed using a median sternotomy. A right axillary artery was used for arterial cannulation, and the right atrium was cannulated with a single atriocaval cannula. A left ventricular drain was inserted through the right upper pulmonary vein. After systemic heparinization (300 U/kg body-weight and maintaining an activated clotting time longer than 480 seconds), cardiopulmonary bypass (CPB) was established. During CPB, temperature-adjusted flow rates of 2.5 L/(min/m²) were used, and the mean arterial pressure was generally maintained between 50 and 70 mmHg. Our institutional preference was to perform total arch replacement using a tetrafurcate vascular graft combined with implantation of a specific stented graft into the descending aorta. The right axillary arterial cannulation for antegrade cerebral perfusion (5–15 mL/[kg/min]) has been previously performed in our hospital. Our policy was to completely excise the primary tear according to the extent of disruption in each patient. The arch was explored under MHCA at a nasopharyngeal temperature between 18°C and 25°C. After completing a distal anastomosis, CPB was reinstated, and the patient was gradually rewarmed to a normal temperature after a 5-minute period of cold reperfusion for free radical washout. A proximal anastomosis was then performed.

2.4. Blood collection

To examine the effect of aortic dissection and surgery on the activation of coagulation and fibrinolysis, blood samples were obtained from all patients at 5 different time points: anesthesia induction (T1), lowest nasopharyngeal temperature (T2), protamine reversal (T3), four hours after surgery (T4), and 24 hours after surgery (T5). The first 5 mL of blood drawn was discarded to eliminate the dilution effect of the saline. The blood samples were stored in a citrated blood collection tube. Blood was taken from the central venous catheter or the peripheral vein and anticoagulated with sodium citrate to measure the coagulation and fibrinolysis. Blood samples were centrifuged for 15 minutes at 3500 rpm at 4°C and frozen at –80°C until assayed.

2.5. Hemostatic system assays

International normalized ratio, white blood cells, hemoglobin, hematocrit, platelet counts, and fibrinogen concentration were

assayed on an automated blood coagulation analyzer. Specific assays were performed to assess the activation of coagulation, anticoagulation, and fibrinolysis. Plasma was assayed by the monoclonal antibody sandwich ELISA technique. Activation of the coagulation system was evaluated by assessing thrombin generation through the thrombin-antithrombin III complex (TAT; normal range: 145.0±40.0 pg/mL) and prothrombin fragment 1+2 (F1+2; normal range: 1.1±0.4 nmol/L). The level of antithrombin III (AT III; normal range: 15.7±4.3 U/mL) was assayed as marker of anticoagulation and the fibrinolysis activation was measured by means of plasminogen (normal range: 470.0±62.0 μg/mL) and the plasmin-antiplasmin complex (PAP; normal range: 38.7±7.3 ng/mL). All ELISA assays were doubled tested, and the mean value was used for analysis.

2.6. Statistical analysis

The normality of the data distribution was tested using the Kolmogorov–Smirnov test. Data were presented as the mean±standard deviation (SD) for continuous data with a normal distribution, as the median (25th percentile, 75th percentile) for continuous data with a nonnormal distribution, or as a number and percentage for categorical values. Differences between time points were analyzed using analysis of variance with repeated measures. Statistical significance was defined at the *p* < 0.05 level, using two-tailed distributions. All statistical analyses were performed using computer software (SPSS 18.0, SPSS, Inc., Chicago, IL).

3. Results

3.1. Baseline characteristics

The preoperative clinical characteristics of the patients are summarized in Table 1. Overall, there were 61 men and 26

Table 1
Preoperative clinical characteristics in patients with acute type A aortic dissection.

Characteristics	Acute type A aortic dissection (n=87)
Age, y	48.6±11.1
Male	61 (70.1)
BMI, kg/m ²	28.4±3.1
Obesity, BMI >30 kg/m ²	14 (16.1)
Hypertension	65 (74.7)
Diabetes mellitus	3 (3.5)
Bicuspid aortic valve	2 (2.3)
Previous cerebral infarction	6 (6.9)
Coronary artery disease	5 (5.7)
Smoking history	35 (40.2)
Alcoholism	13 (14.9)
Marfan syndrome	7 (8.0)
Creatinine, mg/dL	79.5 (65, 95.9)
Tnl, ng/mL	0.02 (0.00, 0.07)
Aortic root size, mm	41.4±8.8
Aortic regurgitation	23 (26.4)
Ascend aorta size, mm	45 (41, 51)
LVEDD, mm	50.6±7.7
LVEF, %	62.5±6.1
Hemopericardium	36 (41.4)
Cardiac tamponade	9 (10.3)
Onset to surgery, hr	48 (24, 168)
D-dimers, ng/mL	1085 (541, 2637)
FDP, mg/L	15.1 (5.7, 31.7)

Values are mean±SD, n (%), or median (interquartile range). BMI=body mass index, FDP=fibrinogen degradation product, LVEDD=left ventricular end-diastolic dimension, LVEF=Left ventricular ejection fraction, Tnl=troponin I.

Table 2	
Surgical procedure and postoperative data.	
Variable	Acute type A aortic dissection (n=87)
Ascending + total-arch replacement	64 (73.6)
Composite graft + total-arch replacement	23 (26.4)
Duration of surgery, hr	9.0 ± 1.7
Duration of CPB, min	200 (163, 239)
Aortic cross clamp time, min	122.9 ± 44.1
Duration of MHCA, min	27.5 ± 9.6
Lowest CPB temperature, °C	22.8 ± 1.9
Reoperation for bleeding	8 (9.2)
Intraoperative blood loss, mL	1400 (1000, 1600)
Total postoperative drainage, mL	2240 (1250, 3760)
Packed red blood cells, mL	900 (600, 1800)
Fresh frozen plasma, mL	400 (200, 800)
Platelet concentrate, mL	300 (0, 600)
In-hospital mortality	9 (10.3%)
Length of in-hospital, day	16.4 ± 3.5
Length of ICU, day	6.8 (1.3, 11.1)
Postoperative dialysis	18 (20.7)
Low cardiac output syndrome	4 (8.1)
Sepsis	10 (11.5)
Paraplegia	4 (8.1)
Respiratory failure	9 (10.3)
Cerebral infarction or bleeding	3 (3.4)

Values are mean ± SD, n (%), or median (interquartile range). CPB = cardiopulmonary bypass, ICU = intensive care unit, MHCA = moderate hypothermic circulatory arrest.

women aged 48.6 ± 11.1 years in the study. Their mean weight and height were 76.1 ± 12.7 kg and 169.1 ± 6.4 cm, respectively. Most of the patients with AAD had chest pain (94.8%) as the predominant preoperative symptom. Hypertension was present in 65 of the 87 patients, and most of these patients had severe

hypertension. All patients were admitted within 14 days of onset of the AAD with an average duration of 48 hours (25%–75% interquartile range [IQR], 24–168 hours).

3.2. Perioperative details

The perioperative clinical details are shown in Table 2. Overall, the types of aortic arch surgery were composite graft or ascending replacement and total arch replacement using a tetrafurcate vascular graft combined with implantation of a specific stented graft into the descending aorta. As expected, patients with AAD required long duration of surgery (9.0 ± 1.7 hours), long duration of CPB (200 minutes [25%–75% IQR, 163–239 minutes]) and long aortic cross clamp time (122.9 ± 44.1 minutes). The postoperative clinical outcome was also complicated in these patients, with a hospital mortality rate of 10.3%. The causes of death were intraoperative acute heart failure in 2 patients and multiple organ failure in 3 patients. In addition, 3 patients died from sepsis and 1 patient suffered respiratory failure. Furthermore, patients with AAD had high rates of postoperative bleeding and blood product transfusion.

3.3. Activation of coagulation

Before surgery, the blood data from the patients with AAD showed that TAT (195.4 ± 32.9 pg/mL) as well as F1 + 2 (2.8 ± 0.6 nmol/L) were elevated above the normal range (Fig. 1 A and B). TAT and F1 + 2 levels were amplified during CPB, reaching tremendously higher levels that were then followed by a gradual increase to 404.1 ± 59.8 pg/mL and 5.6 ± 0.7 nmol/L in the postoperative period, respectively. The surgery was associated with activation of coagulation as reflected by elevated plasma concentrations of TAT and F1 + 2. In contrast, the activation of coagulation observed in patients with AAD was accompanied by

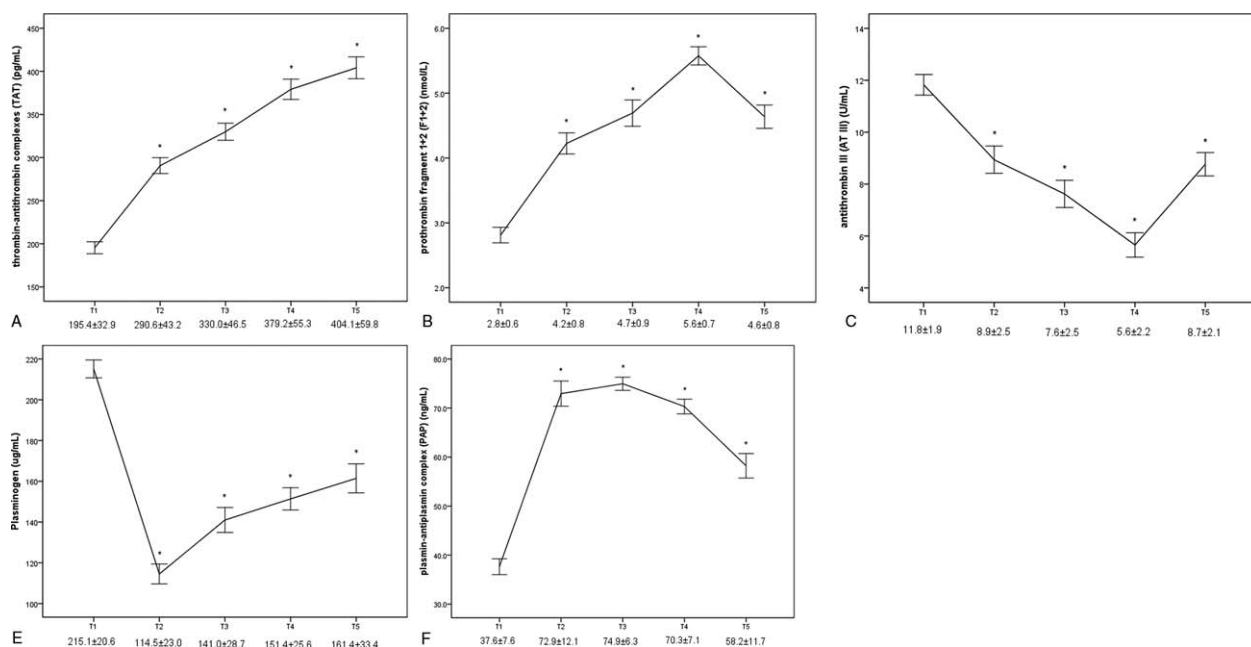


Figure 1. (A) Mean ± SD of thrombin antithrombin (TAT) parameter (pg/mL), (B) F1 + 2 parameter (nmol/L), (C) antithrombin III (AT III) parameter (U/mL), (D) plasminogen parameter (µg/mL), and (E) plasmin-antiplasmin complex (PAP) parameter (ng/mL) in AAD; the data within 24 hours after surgery were unavailable for 3 patients. (T1 = anesthesia induction; T2 = lowest nasopharyngeal temperature; T3 = protamine reversal; T4 = 4 hours after surgery; T5 = 24 hours after surgery.) The statistical results were analyzed by analysis of variance with repeated measures (*P* < 0.01 compared with anesthesia induction).

Table 3
Standard laboratory tests at 5 time points.

Variable Point	Anesthesia induction	Lowest nasopharyngeal temperature	Protamine reversal	4 hours after surgery	24 hours after surgery
INR	1.0±0.1	NA	4.4±1.3*	1.2±0.2	1.2±0.2
White blood cells, ×10 ³ cells/μL	16.7±4.1	3.7±2.4*	10.8±5.5*	10.8±4.7*	15.1±6.2
Hemoglobin, g/dL	136.7±18.1	77.0±15.1*	89.2±15.1*	97.4±21.6*	91.4±18.7*
Hematocrit, %	39.5±4.8	22.9±4.4*	26.2±4.3*	28.7±6.4*	26.9±5.5*
Platelet counts, ×10 ³ cells/μL	180.0±70.9	70.5±38.1*	97.8±45.7*	91.9±64.6*	87.6±56.2*
Fibrinogen, g/L	3.5±1.6	1.3±0.6*	2.0±1.0*	2.6±1.2*	3.5±1.3

Data within 24 hours after surgery were unavailable for 3 patients. Values are mean±SD or median (interquartile range). INR=international normalized ratio, NA=not applicable.

**P*<0.01 compared with anesthesia induction.

depression of anticoagulation. AT III levels gradually declined during surgery and decreased to the lowest level (5.6±2.2 U/mL) in the postoperative period (Fig. 1C).

3.4. Activation of fibrinolysis

The change in plasminogen levels showed the lowest value of 114.5±23.0 μg/mL at the time of the lowest nasopharyngeal temperature (T2) with a subsequent rise (*P*<0.01) to a level of 161.4±33.4 μg/mL by 24 hours after surgery. However, all these levels were still significantly lower than the upper limits of normal during the observation period (Fig. 1D). The PAP levels also displayed a fairly similar pattern with coagulation. The PAP levels dramatically increased to very high values (74.9±6.3 ng/mL) during surgery followed by a decline to 58.2±11.7 ng/mL within 24 hours after surgery (Fig. 1E).

3.5. Standard laboratory tests

The results of standard laboratory tests are shown in Table 3. Preoperative routine assays demonstrated high D-dimer levels and fibrinogen degradation product levels in patients with AAD. During CPB, white blood cells, hemoglobin, hematocrit, and platelet counts were significantly decreased compared with baseline values (*P*<0.01). Nevertheless, hemoglobin, hematocrit, and platelet counts remained at low levels within 24 hours after surgery (*P*<0.01). In this study, all analyzed patients exhibited hypofibrinogenemia and their fibrinogen levels frequently decreased to <1.5 g/L during CPB. After hemostatic therapy, the fibrinogen level increased gradually and returned to baseline values within 24 hours after surgery.

4. Discussion

Our study systematically and comprehensively describes the systemic activation of coagulation and fibrinolysis, and inhibition of the anticoagulation pathway in patients underwent surgery within 24 hours of the onset of AAD in this emergency situation. A few studies have focused on this topic^[3,6] but none of them has systematically described the state of patients with AAD before, during, and immediately after the emergent surgery.

The principal finding of the present study is that emergent surgery for AAD is associated with intense thrombin generation (as demonstrated by elevated TAT and F1+2 levels, and by suppressed AT III) and excessive systemic fibrinolysis (as demonstrated by decreased plasminogen and elevated PAP complex). This procoagulant state is present before surgery and persists throughout the period of surgery when under the influence of MHCA. In fact, AAD itself is frequently associated

with a high risk for coagulation disorders, and aortic arch surgery with MHCA inevitably results in excessive bleeding and transfusion of allogeneic blood products. If this procoagulant state is prolonged, active consumption coagulopathy may cause serious complications such as DIC and multiple organ failure.

In cases of AAD, there is damage to the intima with formation of a false lumen in the aorta media. Preoperatively, elevated levels of TAT and F1+2 may be related to the presence of thrombi within the false lumen. After an initial burst, blood flow through the false lumen causes a subsequent activation of coagulation and secondary increased fibrinolytic activity even before surgery.^[3] The possible underlying mechanism for activation of coagulation is blood contact with tissue factor-secreting fibroblasts of the adventitia and smooth muscle cells, which results in the release of large amounts of tissue thrombokinase and plasminogen activators. Thus, we have reason to believe that this preoperative procoagulant state may be related to AAD itself, immediately after the onset of aortic dissection.

As expected in this study, TAT and F1+2 levels in all patients dramatically increased during surgery. The surgery with CPB is generally regarded as the valid trigger for the activation of coagulation in cardiac surgery.^[7,8] In our study, the elevated levels of TAT and F1+2 reflected excessive thrombin generation owing to blood and CPB surface interactions with a complexity of regulatory process during surgery. Thrombin plays, in fact, a central role in CPB-induced coagulopathy.^[9,10] Thrombin regulates various biochemical and physiologic processes in coagulation and inflammation. There is a great deal of researches^[11,12] showing that thrombin promotes clotting factor consumption and excessive fibrinolysis, resulting in increased postoperative blood loss and blood product transfusion. In addition, thrombin is the most powerful platelet activator in vivo and can be considered one of the main causes of platelet dysfunction.^[10] Thus, we speculated that massive thrombin generation before and during surgery was a possible underlying mechanism contributing to the coagulopathy and bleeding in patients with AAD. It has been suggested that reducing thrombin generation in CPB may result in decreased blood loss and transfusion volumes.^[13]

Therefore, we believed that excessive thrombin generation caused the consumption coagulopathy and the formation of many thrombi. This procoagulant state may contribute to the microvascular and macrovascular thrombotic events that lead to cerebral and myocardial infarctions, multiple organ failure and thromboembolism.^[6,14] Similarly, systemic HCA also accelerates microvascular thrombus formation in arterioles and venules in mice.^[15] Thus, we speculated that this thrombotic tendency might cause consumption coagulopathy by activating coagulation cascades. We already confirmed consumption coagulopathy

in the acute phase of AAD by thromboelastography throughout the observation period.^[16] This consumption coagulopathy was consistent with the decreases in platelet counts and fibrinogen levels in our study, along with a remarkable increase in coagulation and fibrinolysis. The combination of decreased fibrinogen levels and platelet counts was also considered 1 of the 2 most sensitive measures of clinical coagulopathy.^[17]

In addition to having a powerful inhibitory action on thrombin, AT III also has anti-inflammatory properties.^[18] AT III deficiency can be encountered in sepsis, after major trauma or surgery, or in DIC.^[19] Similarly, we found that the AT III levels had been transiently inhibited during surgery, and fibrin formation did occur in our study. Our finding was that reduction of AT III activity during MHCA could possibly aggravate local aortic inflammation, increase thrombotic tendency, and worsen the prognosis of the patients.^[20–22] Because clot formation away from the site of the injury is subject to inhibition by AT III, enhanced thrombin generation and AT III consumption in these patients contribute to a procoagulant state, leading to clinical complications such as myocardial and cerebral infarctions, multiple organ failure or DIC.^[18,19,23] Additionally, lower AT III levels identified AAD patients with an excessively increased risk for early mortality or adverse outcomes.^[24] Although our findings in an observational cohort study did not prove a causal relationship between AT III activity and the occurrence of adverse events, this issue should be further investigated. We speculated that AT III supplementation would be beneficial for these patients and that measurement of preoperative AT III activity might provide new insights.

The fibrinolysis was more extremely activated in patients with AAD during surgery despite antifibrinolytic prophylaxis. The secondary increased fibrinolytic activity is associated with postoperative bleeding^[12] and can be a cofactor leading to hemorrhagic complications. In patients with AAD, even before surgery, thrombin generation stimulates plasminogen activator release through activation of the coagulation cascade to cause secondary excessive fibrinolysis, which may continue during CPB despite full heparinization. Consequently, fibrinolysis that disrupts thrombus formation and clotting factor consumption leads to fatal DIC and bleeding.

Taking all these factors into consideration, we should consider the patients with AAD to be at high risks for perioperative coagulopathy and the necessity of massive blood transfusion. The changes in hemostatic system clearly indicated the presence of a blood coagulation disorder, which necessarily triggered a DIC-like syndrome. Our data seem to suggest that the preservation of the hemostatic system should be one of the objectives in the surgical treatment of AAD. Nevertheless, the emphasis during surgery is toward preventing endothelial cell ischemia and microvascular thrombus formation. Theoretically, thrombin generation should be reduced perioperatively but the anticoagulation of patients with an elevated hemorrhagic risk is a difficult task. Therefore, basic scientific principles for this DIC-like state would appear to suggest the use of different medications for different phases of AAD.

4.1. Study limitations

This preliminary study had several limitations. First, the study did not include a control group. It would be useful to have a control group, consisting of patients undergoing elective complex repairs of the ascending aorta and aortic arch, to highlight the differences in the coagulation between patients with AAD and patients

requiring complex CPB surgery. In addition, at the second sample time (T2), it was difficult to separate the effects of the false lumen and from those of extended CPB, hypothermia, and copious blood product transfusion. With the experience gained in past years and from the results of this study, the present authors designed a prospective clinical trial to determine the coagulation and fibrinolysis in patients with AAD compared with patients requiring complex CPB surgery. Third, this is an observational single-center prospective study, which makes it subject to inherent selection and information biases. The patients with comorbidities might cause the data in perioperative hemostatic system deviation. However, the prospective nature of the data collection and the low rate of missing data (<5%) add strength to the internal validity of our study.

5. Conclusions

In conclusion, AAD itself is associated with an intense activation of hemostatic system. During surgery with CPB, this reaction is enormously amplified, possibly explaining the coagulopathy frequently observed. These novel data demonstrate that patients with AAD exhibit consumption coagulopathy perioperatively because of systemic activation of hemostatic system and inhibition of the anticoagulation pathway. This procoagulant state may contribute to microvascular and macrovascular thrombosis that, in turn, lead to the common causes of perioperative morbidity and mortality. Therefore, we believe that this remarkable DIC-like coagulopathy has a high risk of bleeding and may influence the postoperative outcomes of patients with AAD.

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