

Low preoperative fibrinogen level is risk factor for neurological complications in acute aortic dissection

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Abstract

Aortic arch surgery in patients with acute aortic dissection is frequently complicated by neurological complications and coagulopathy. However, the relationship between the coagulation system and neurological complications in patients with acute aortic dissection has not been clarified. Thus, the aim of this study was to investigate the relationship between the coagulation system and neurological complications in patients with acute aortic dissection.

From September 2014 to January 2016, a total of 126 patients with acute type A aortic dissection were enrolled. Perioperative characteristics and standard laboratory tests upon admission were analyzed using univariate and multivariate logistic regression analysis in this study. The primary outcome was the correlation between the coagulation system and neurological complications.

Univariate logistic regression analysis showed that the neurological complications (+) group underwent more serious and complicated postoperative outcomes. Multivariable logistic regression analysis revealed serum creatinine level (OR, 1.049; 95% CI, 1.011–1.089; $P=.01$), white blood cell counts (OR, 1.581; 95% CI, 1.216–2.057; $P=.001$) and fibrinogen concentration upon admission (OR, 0.189; 95% CI, 0.060–0.596; $P=.004$) as predictors of neurological complications. However, we found that there was no association between the coagulation system and in-hospital mortality.

Low preoperative fibrinogen level is the preferred marker for predicting clinical neurological complications in patients with acute type A aortic dissection treated with surgical repair.

Abbreviations: AAD = acute aortic dissection, AUC = area under the curve, CI = confidence interval, CPB = cardiopulmonary bypass, OR = odds ratio, ROC = receiver operating characteristic.

Keywords: acute aortic dissection, coagulation system, fibrinogen, neurological complication

1. Introduction

Acute aortic dissection (AAD) is a devastating cardiovascular disease with considerable mortality and severe postoperative

complications, especially in patients with acute type A aortic dissection (according to the Stanford classification system). Although the introduction of selective antegrade cerebral perfusion has improved surgical results in many aortic centers, many reports still show relatively high neurological complications^[1,2] and high incidences of coagulopathy^[3,4] after surgical treatment.

In recent decades, studies have shown that coagulopathy occurred in up to one-third of patients after major cardiothoracic surgery. As the final substrate in the coagulation cascade, fibrinogen plays a key role in effective coagulation and clot formation. However, the relationship between the coagulation system and neurological complications in patients with AAD has not been clarified. Thus, our objective was to assess the association between the preoperative fibrinogen levels and neurological complications in patients with AAD undergoing aortic arch surgery with hypothermic circulatory arrest.

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2. Methods

2.1. Study population

A total of 126 patients with proven Stanford type A AAD who underwent emergent aortic arch surgery with hypothermic circulatory arrest from September 2014 to January 2016 at Anzhen Hospital were retrospectively registered. The diagnosis of AAD was confirmed in all patients using multidetector computed tomography. AAD was defined as acute if the time from the onset of the symptoms to admission was within 14 days.^[5] Patients

were recruited consecutively basis, if they agreed to provide informed consent.

Exclusion criteria included patients with subacute and chronic type A aortic dissection, intramural hematomas, penetrating aortic ulcers, traumatic aortic transection, and death prior to planned surgery. Moreover, those who recently had a surgery or infectious diseases were also excluded. The study protocol was approved by the Anzhen Hospital Ethics Committee (Institutional Review Board File 2014019), and consent was obtained from the patients or their relatives. All procedures were performed by a single surgical team.

2.2. Study groups

The patients were categorized into 2 groups according to their neurological complications. For each patient, clinical baseline characteristics, risk factors for neurological complications, biochemical and hematologic laboratory data, and all clinical outcomes were obtained by reviewing the patient's chart from the database of the hospital. In this study, venous blood samples were collected at the time of admission to the Emergency Department and were sent to the laboratory within minutes of collection.

2.3. Study endpoint definitions

The primary end-point was the rate of neurological complications during hospitalization. The neurological complications consisted of permanent neurological dysfunction and temporary neurological dysfunction.^[6] Permanent neurological dysfunction was defined as the presence of a new postoperative focal (stroke) or global (Parkinsonism, coma or gait disturbance) neurological deficit that persisted at discharge. Temporary neurological dysfunction was defined as the occurrence of postoperative agitation, confusion, delirium, obtundation, or a transient focal neurologic deficit (resolution within 72 hours) without any evidence of a new structural abnormality via computed tomography or magnetic resonance imaging.

2.4. Surgical procedures

The types of aortic arch surgery performed were composite graft or ascending replacement + total arch replacement using a tetrafurcate vascular graft in combination with the implantation of a special stented graft into the descending aorta. Standard anesthetic management was used with endotracheal intubation. The procedures were performed via median sternotomy. The right axillary artery was used for arterial cannulation, and the right atrium was cannulated with a single atriocaval cannula. After systemic heparinization (300 U/kg body weight and maintenance of an activated clotting time of longer than 480 seconds), cardiopulmonary bypass (CPB) was established. CPB and systemic cooling were initiated, and once the heart fibrillated, a vent was placed into the left ventricle via the right superior pulmonary vein. 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 mm Hg. The proximal aortic procedures, as well as any coronary or valve interventions, were completed. Upon reaching the goal nasopharyngeal temperature, the pump was switched off and the patient was drained. Right axillary arterial cannulation for antegrade cerebral perfusion (5–15 mL/[kg min]) has been done in our hospital. The transverse arch was replaced under moderate hypothermic circulatory arrest at a nasopharyngeal temperature

between 18°C and 28°C. After finishing the distal anastomosis, CPB was reinstated, and the patient was gradually rewarmed to a normal temperature.

2.5. Statistical analysis

The normality of the data distribution was determined using the Kolmogorov–Smirnov test. Data are presented as the mean ± standard deviation (SD) for continuous data with a normal distribution, the median (25th percentile, 75th percentile) for continuous data with a non-normal distribution, or a percentage for categorical values. For comparisons, the two-tailed Student *t* test was used for continuous variables with a normal distribution, while the nonparametric Wilcoxon rank-sum test was used for non-normal distributions. The Chi-square test or Fisher's exact test was used for categorical variables. A *P* value of <0.05 was defined for selecting variables for use in the final multivariable stepwise logistic regression model for the analysis of risk factors for neurological complications. Adjusted risk factors were estimated with an odds ratio (OR) and 95% confidence interval (CI) with a logistic regression. A receiver operating characteristic (ROC) curve analysis was performed to detect the best cut-off value for the fibrinogen concentration in the prediction of neurological complications. Statistical significance was defined at the <0.05 level and using two-tailed distributions. All statistical analyses were performed with SPSS 18.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Perioperative clinical characteristics

The perioperative clinical characteristics of the study subjects are shown in Table 1. A total of 126 patients with AAD (mean age, 49.1 ± 11.4 years; 96 men and 30 women) were enrolled. Of these, 19 (15.1%) had a temporary neurological dysfunction and 11 (8.7%) had a permanent neurological dysfunction during hospitalization. Of those who experienced neurological complications, approximately one-half, died during hospitalization, which resulted in a high in-hospital mortality rate.

There were no significant differences in the baseline characteristics between the 2 groups except for smoking history and drinking history (*P* = .09 and *P* = .01). Levels of serum creatinine, white blood cells and D-dimer were higher in the neurological complications (+) group compared to those of the neurological complications (–) group (*P* < .01). In contrast, patients in the neurological complications (+) group had significantly lower preoperative platelet counts and fibrinogen concentrations (*P* = .01 and *P* < .01). Although the pathological backgrounds were completely different, a subgroup analysis showed that there was no significant difference in the fibrinogen concentration between the permanent neurological dysfunction group and the temporary neurological dysfunction group (2.6 ± 0.7 vs 3.5 ± 1.9 g/L, *P* = .16).

In addition, there was significant difference in the operation time and CPB time between the 2 groups (9.6 ± 2.0 vs 8.3 ± 1.9 hours, *P* < .01; 240.5 ± 69.7 vs 207.6 ± 51.5 minutes, *P* < .01). However, the aortic cross clamp time and the duration of hypothermic circulatory arrest were similar between the groups (*P* > .05). Moreover, the neurological complications (+) group had a significantly higher rate of packed red blood cells and platelet concentrate transfusion than the neurological complications (–) group (*P* < .01).

Table 1
Perioperative data according to study groups.

Variable	Neurological complications (+) (n=30)	Neurological complications (-) (n=96)	P
Baseline characteristics			
Age, years	48.9±10.1	47.2±10.2	.43
Male	21 (70.0)	75 (78.1)	.36
BMI, kg/m ²	27.3±3.1	25.7±4.0	.05
Hypertension	26 (86.7)	80 (83.3)	.88
Diabetes mellitus	2 (6.7)	6 (6.3)	1.00
Bicuspid aortic valve	1 (3.3)	6 (6.3)	.88
Previous neurological disease history	2 (6.7)	6 (6.3)	1.00
Peripheral vessel disease	2 (6.7)	5 (5.2)	.67
Hyperlipidemia	1 (3.3)	4 (4.2)	1.00
COPD	0	2 (2.1)	1.00
Coronary artery disease	1 (3.3)	4 (4.2)	1.00
Atrial fibrillation	3 (10.0)	9 (9.4)	.92
Smoking history	19 (63.3)	44 (45.8)	.09
Drinking history	11 (36.7)	15 (15.6)	.01
Marfan syndrome	3 (10.0)	5 (5.2)	.61
Onset to surgery, hour	24 (17, 48)	31 (24, 72)	.07
Ultrasonographic cardiogram			
Aortic regurgitation	6 (20.0)	20 (20.8)	.92
Left ventricular ejection fraction, %	64.5±6.2	62.5±5.7	.12
Aortic root size, mm	42.5±6.5	40.6±8.0	.28
Ascend aorta size, mm	45.8±6.8	45.9±8.4	.95
Computed tomography			
Involvement of the supra-aortic branches	9 (30.0)	30 (31.2)	.90
Above the level of diaphragmatic hiatus	7 (23.3)	22 (22.9)	.96
Standard laboratory tests on admission			
Serum creatinine, mg/dL	107.4±36.2	78.4±19.9	<.01
Troponin I, ng/mL	0.04 (0.00, 0.08)	0.03 (0.00, 0.08)	.64
White blood cells, × 10 ³ /μL	13.5±4.3	11.1±3.2	<.01
Hemoglobin, g/dL	135.8±15.9	134.8±16.8	.77
Platelet counts, × 10 ³ /μL	143.8±41.1	182.0±77.0	.01
Fibrinogen concentration, g/L	2.5±0.5	3.8±1.8	<.01
D-dimer, ng/mL	2397 (1129, 2856)	1085 (661, 2472)	<.01
Surgical procedures			
Ascending + total-arch replacement	12 (40.0)	38 (39.6)	.97
Composite graft + total-arch replacement	18 (60.0)	58 (60.4)	.97
Operation time, hours	9.6±2.0	8.3±1.9	<.01
CPB time, min	240.5±69.7	207.6±51.5	<.01
Aortic cross clamp time, minutes	134.9±34.2	122.5±42.9	.15
The duration of HCA, minutes	28.4±7.1	26.9±9.6	.45
Intraoperative blood loss, mL	1600 (1150, 2000)	1300 (1000, 1700)	.19
Total postoperative drainage, mL	1790 (1290, 2220)	2442 (1340, 3837)	.14
Packed red blood cells, mL	1800 (825, 3000)	900 (600, 1400)	<.01
Fresh frozen plasma, mL	600 (400, 1200)	600 (400, 1000)	.24
Platelet concentrate, mL	300 (0, 600)	0 (0, 300)	<.01
Postoperative outcomes			
In-hospital mortality	17 (56.7)	6 (6.3)	<.01
Length of in-hospital, day	17 (11, 22)	14 (10, 17)	.04
Length of ICU, day	8.8 (3.9, 14.8)	2.0 (1.0, 4.0)	<.01
Reoperation for bleeding	5 (16.7)	4 (4.2)	.05
Postoperative dialysis	17 (56.7)	10 (10.4)	<.01
Low cardiac output syndrome	4 (13.3)	4 (4.2)	.17
Sepsis	11 (36.7)	8 (8.3)	<.01
Paraplegia	4 (13.3)	3 (3.1)	.55
Respiratory failure	13 (43.3)	7 (7.3)	.06

Values are mean±SD, n (%), or median (interquartile range).

BMI=body mass index; COPD=chronic obstructive pulmonary disease; CPB=cardiopulmonary bypass; HCA=hypothermic circulatory arrest; ICU=intensive care unit; SD=standard deviation.

Postoperative clinical outcomes were also complicated in these patients with neurological complications. The in-hospital mortality rate was 56.7% (17/30) in the neurological complications (+) group, clearly higher than that of the neurological

complications (-) group ($P < .01$). Similarly, the frequencies of both postoperative dialysis (56.7% vs 10.4%, $P < .01$) and sepsis (36.7% vs 8.3%, $P < .01$) were significantly higher in the neurological complications (+) group. In addition, patients with

Table 2**Risk factors for neurological complications in multivariate logistic regression analysis.**

Risk factors	OR	95% CI	P
Serum creatinine, mg/dL	1.049	1.011–1.089	.010
White blood cells, $\times 10^3/\mu\text{L}$	1.581	1.216–2.057	.001
Fibrinogen, g/L	0.189	0.060–0.596	.004

CI = confidence interval; OR = odds ratio.

AAD in the neurological complications (+) group required a longer length of in-hospital and intensive care unit care ($P = .04$ and $P < .01$).

3.2. Multivariable logistic regression analysis

In the primary model, all preoperative risk factors, intraoperative parameters of recognized clinical significance and standard laboratory tests upon admission were included ($P < .05$). Multivariable logistic regression analysis revealed that serum creatinine level (OR, 1.049; 95% CI, 1.011–1.089; $P = .010$), white blood cell counts (OR, 1.581; 95% CI, 1.216–2.057; $P = .001$) and fibrinogen concentration (OR, 0.189; 95% CI, 0.060–0.596; $P = .004$) were predictors of neurological injury (Table 2). However, we did not find an association between fibrinogen concentration and permanent neurological dysfunction or temporary neurological dysfunction by multivariable logistic regression analysis ($P = .23$ and $P = .19$).

ROC curve analysis was performed to detect the best cut-off value for the fibrinogen concentration in the prediction of neurological complications. Fibrinogen concentration < 3.425 g/L yielded an area under the curve (AUC) value of 0.744 (95% CI

0.650–0.837, $P < .001$). Furthermore, the fibrinogen concentration demonstrated a sensitivity of 100% and a specificity of 51.9% for the prediction of neurological injury (Fig. 1).

In addition, we found that the rate of neurological complications in fibrinogen concentration < 3.425 g/L groups was higher than fibrinogen concentration > 3.425 g/L groups ($p = 0.001$) (Fig. 2). Although we found a similar trend in in-hospital mortality between 2 groups ($P = 0.04$) (Fig. 2), we did not find that fibrinogen concentration was a risk factor for in-hospital mortality.

4. Discussion

The present study, based on a cohort of patients with type A AAD, highlights the relevance of reduced fibrinogen concentration upon admission with a neurological injury. Low preoperative fibrinogen level may be valuable as a predictor of neurological complications, and may be useful in the risk stratification of AAD during hospitalization.

Acute type A aortic dissection represents a catastrophic event with a very high risk of mortality and morbidity. Neurological complications of aortic arch surgery have gained increasing attention, and some surgeons believe that these mortality and morbidity rates are mainly caused by hypothermic circulatory arrest.^[7] In our study, no risk factors associated with surgery could be identified for neurological complications. Thus, we suggest that the hypothermic circulatory arrest time is not a risk factor for neurological complications in aortic arch surgery, which is inconsistent with findings reported by others.^[8,9] In these investigations, the hypothermic circulatory arrest time was a significant predictor of stroke or temporary neurological dysfunction. A possible explanation for this difference might be the fact that the hypothermic circulatory arrest time exceeded 30 and 50 minutes in only 47 (37.3%) and 3 (2.4%) of our

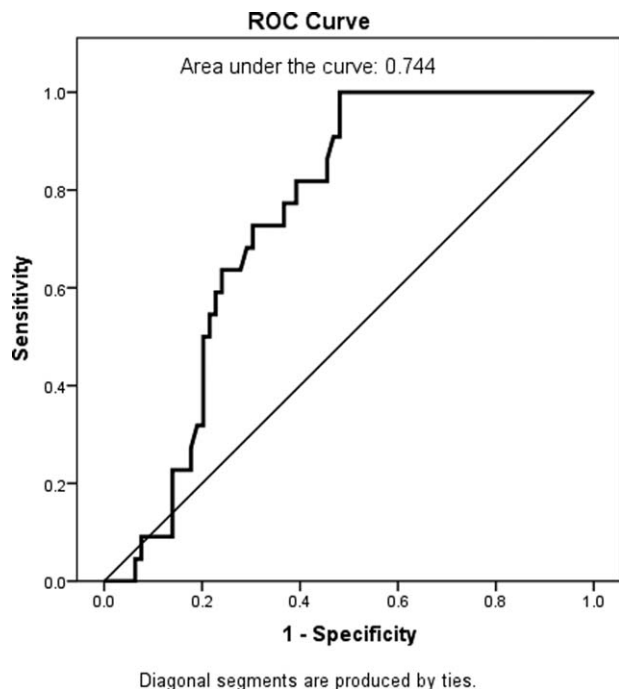


Figure 1. It depicts the results of receiver operating characteristic (ROC) curve analysis for the value of preoperative fibrinogen concentrations in the prediction of neurological complications in patients with acute type A aortic dissection.

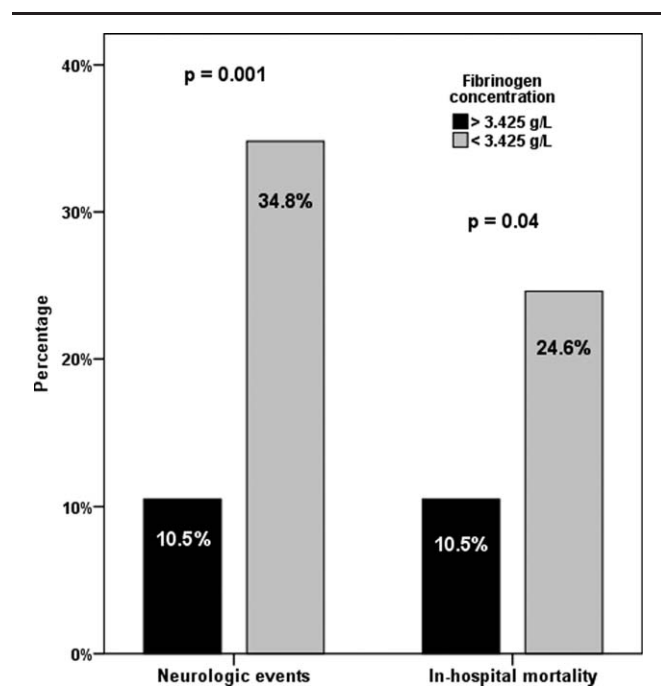


Figure 2. The results of the percentiles of neurological injury and in-hospital mortality in terms of cut-off value of the fibrinogen concentration in patients with acute type A aortic dissection.

patients, respectively. With a prolonged hypothermic circulatory arrest time of 45 minutes or longer, the risk of neurological deficit will increase considerably. Increasing experimental and clinical evidence^[8,10] has suggested that the safety limit of hypothermic circulatory arrest might be approximately 30 to 40 minutes. Thus, we speculated that hypothermic circulatory arrest time (< 30 minutes) did not influence the incidence of neurological complications at all.

It is well known that neurological complications are associated with longer ventilation times and prolonged intensive care unit and hospital lengths of stay for cardiac surgery. Embolism of air, calcium, or atherosclerotic debris might result in stroke independent of circulatory arrest. Thus, there are multiple potential risk factors for neurological complications, particularly in aortic arch surgery. Coagulopathy for AAD is a well-known clinicopathological entity in patients with AAD. Through the above analysis of our data, we speculated that neurological injury might be caused by consumption coagulopathy. After an initial burst, blood flow through the false lumen causes an activation of the coagulation system during the early stage of AAD. Previous investigations^[11] have already shown that AAD itself activated the coagulation system before surgery. Therefore, excessive fibrinogen consumption and the formation of many thrombi lead to a subsequent procoagulant state. If this procoagulant state is prolonged, this coagulopathy may contribute to microvascular and macrovascular thrombotic complications, such as disseminated intravascular coagulation and neurological injury.^[12,13] This consumption coagulopathy likely increases the incidence of embolism, which will result in neurological complications.

As the final substrate in the coagulation cascade and the ligand of the platelet GP IIb/IIIa receptors, fibrinogen plays a key role in effective coagulation, platelet function and clot formation.^[14,15] Administration of fibrinogen has been shown to improve clot firmness and reduce blood loss in experimental studies using pig models.^[16] Furthermore, several recently published trials and systematic reviews^[17,18] have suggested that fibrinogen therapy may be effective in controlling perioperative bleeding and reducing transfusion requirements as well as postoperative drainage volumes. A decreased fibrinogen level was also considered to be one of the most sensitive measures of clinical coagulopathy. However, the relationships between admission fibrinogen concentrations and neurological complications in patients with AAD have not been clarified.

Fibrinogen or fibrin plays overlapping roles in coagulation, the inflammatory response and tissue repair functions. Although there has been considerable evidence^[19,20] to support fibrinogen supplementation in patients undergoing CPB, excessive fibrinogen supplementation during an operation might lead to nervous system damage resulting from considerable fibrinogen leakage in patients with low preoperative fibrinogen levels. In 1995, Bugge et al^[21] had shown that the sustained deposition of fibrin in tissues is sufficient to cause wasting and tissue necrosis in mice genetically deficient for plasminogen. Several studies^[22,23] also showed that fibrinogen could extravasate in the nervous system and exacerbate subsequent edema formation and neuronal damage after injury or disease. Therefore, the fibrinogen-induced signal transduction pathways play a great role in nervous system pathology. In addition, peripheral nerve injury was also exacerbated in tissue plasminogen activator-deficient or plg^{-/-} mice,^[24] which have increased fibrin deposition. These observations showed a deleterious role of intravascular fibrin deposition in inhibiting neurite outgrowth and hampering central nervous system repair. Considerable fibrinogen administration in patients

with AAD resulted in excessive fibrin formation and deposition. Thus, in this setting, fibrin deposition might be the cause of neurological complications in patients with low fibrinogen levels.

White blood cells and their subtypes are widely known as classic inflammatory biomarkers that predict cardiovascular outcomes. A recent study^[25] has shown that inflammation plays an important role in the dissection of the aorta, from the development to the prognosis of AAD. White blood cell counts upon admission may have an impact on the short- and long-term outcomes of AAD. Inflammation has been reported to be associated with AAD. Acute aortic dissection might promote an inflammatory cascade and internal opiate that will be detrimental to ischemia-reperfusion injury in the central nervous system during aortic surgery. In the present study, we thus evaluated white blood cell levels upon admission in patients with AAD and demonstrated the clinical implication of white blood cells in AAD.

5. Study limitations

The limitations of our study were as follows: This was a nonrandomized, single center study that included a relatively small number of patients who were retrospectively enrolled from our database; this study might be subject to selective bias. Second, our conclusion in this study relies heavily upon statistical methods to eliminate biases in patient selection and treatment, and the results should be interpreted with consideration of this limitation. Third, potential confounders (e.g., the extent of dissection or the time from the onset of symptoms) may not have been adequately controlled in this study. Any investigation focusing on the possible detrimental effects of neurological complications must take other potential risk factors into consideration.

6. Conclusions

In summary, low preoperative fibrinogen levels may be a valuable predictor of neurological complications and may be useful in the risk stratification of AAD during hospitalization. Excessive fibrinogen leakage and fibrin deposition might be the cause of neurological complications in patients with AAD. Thus, we propose that it is important to properly supplement fibrinogen in patients with AAD.

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