



# The incidence and risk factors of hypofibrinogenemia in cardiovascular surgery

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Received: 16 March 2019 / Accepted: 4 September 2019 / Published online: 17 September 2019  
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## Abstract

**Objective** Cardiovascular surgery often causes massive bleeding due to coagulopathy, with hypofibrinogenemia being a major causative factor. We assessed the intraoperative incidence of hypofibrinogenemia and explored predictors of hypofibrinogenemia.

**Methods** The intraoperative serum fibrinogen level (SFL) was routinely measured in 872 consecutive patients [mean age:  $66.9 \pm 13.3$  years; 598 men (68.6%)] undergoing cardiovascular surgery from July 2013 to November 2016 at Nagoya University Hospital. There were 275 aortic surgeries, 200 cases of coronary artery bypass grafting (CABG), 334 valvular surgeries and 63 other surgeries. We estimated hypofibrinogenemia incidence (intraoperative lowest SFL  $\leq 150$  mg/dL) and identified its predictors by a logistic regression analysis.

**Results** The average intraoperative lowest SFL of all cases, aortic surgery, CABG and valvular surgery was  $185 \pm 71$ ,  $156 \pm 65$ ,  $198 \pm 69$  and  $198 \pm 68$  mg/dL, respectively. Aortic surgery had a significantly lower intraoperative lowest SFL than CABG ( $p < 0.001$ ) and valvular surgery ( $p < 0.001$ ). The incidence of hypofibrinogenemia was 32.8%, 50.2%, 26.5% and 22.8% in all cases, aortic surgery, CABG and valvular surgery, respectively. The predictors of hypofibrinogenemia were the preoperative SFL, re-do surgery and perfusion time. A receiver operating characteristics curve analysis showed that the best preoperative SFL cutoff value for predicting hypofibrinogenemia was 308.5 mg/dL. Assuming preoperative SFL 300 mg/dL as the cutoff, the odds ratio for hypofibrinogenemia was 7.22 (95% confidence interval 5.26–9.92,  $p < 0.001$ ).

**Conclusions** The incidence of hypofibrinogenemia in aortic surgery was high. The preoperative SFL, re-do surgery and perfusion time were identified as predictors for hypofibrinogenemia. Intraoperative measurement of SFL is important for detecting hypofibrinogenemia and applying appropriate and prompt transfusion treatment.

**Keywords** Fibrinogen · Cardiovascular surgery · Coagulopathy · Hemostasis

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s11748-019-01201-8>) contains supplementary material, which is available to authorized users.

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## Introduction

Cardiovascular surgery is often associated with excessive perioperative bleeding due to intraoperative coagulopathy. The bleeding tendency is associated with numerous factors; however, the consumption of coagulation factors, especially fibrinogen, is a main factor. Therefore, hypofibrinogenemia is a key factor associated with coagulopathy during cardiovascular surgery. It is useful to measure the intraoperative serum fibrinogen level (SFL) during cardiopulmonary bypass (CPB) to prepare for blood transfusion and the need for blood products. Most studies on the perioperative SFL in cardiovascular surgery have focused on only one kind of surgery, such as coronary artery bypass grafting (CABG) or

aortic surgery [1–8], with few studies comparing the SFL among aortic surgery, CABG and valvular surgery.

This study assessed the incidence of hypofibrinogenemia and explored the predictors of hypofibrinogenemia in cardiovascular surgery.

## Materials and methods

The baseline characteristics of the overall population are shown in Table 1. A retrospective study was conducted on 1004 consecutive patients who underwent cardiovascular operations between July 2013 and November 2016 at Nagoya University Hospital. We excluded 5 procedures (0.5%) due to missing data and 127 off-pump procedures (12.6%), resulting in a study cohort of 872 procedures. Urgent operation was defined in cases starting within 24 h from the decision to perform surgery being made, while emergent operation was defined in cases starting as soon as the decision was made.

Anesthesia and surgical treatment were performed according to the standard procedures of our institute. This included the intraoperative use of cell saver. The standard priming volume of our extracorporeal circulation circuit is 1100 mL, consisting of Ringer's bicarbonate 800 mL

and mannitol 300 mL. CPB was established after a loading dose of 300 IU/kg of unfractionated heparin plus additional doses to reach and maintain a target activated clotting time of  $\geq 400$  s. After the completion of main procedure, protamine sulfate was administered at a dose to achieve near-preoperative ACT values. Hypothermia, which may be related to coagulopathy, has been applied for brain protection and organ protection in some aortic surgery cases. Selective cerebral perfusion is mainly used for total aortic arch replacement under deep hypothermia around 25 °C. When aortic cross-clamping could be applied, the aortic root surgery or proximal ascending aorta replacement required no intentional hypothermia. Descending and/or thoracoabdominal aortic replacement was mainly performed with partial bypass under mild hypothermia.

The SFL was measured by the Clauss method at our institute. In operations with CPB, the SFL was measured routinely at the end of CPB and additionally measured at the discretion of the anesthesiologist when coagulation disorder occurred. The administration of blood products, including fibrinogen concentrate, was considered before reversing heparin with protamine sulfate. Blood transfusion protocol in our hospital was described in supplement Fig. 1.

At our institute, the administration of fibrinogen concentrate is approved by our institutional ethics

**Table 1** Baseline characteristics of the patients

| Variables   | All patients (N=872) | Aortic surgery (N=275) | CABG (N=200) | Valvular surgery (N=334) | p value |
|---|----------------------|------------------------|--------------|--------------------------|---------|
| Age (years)                                       | 66.9 ± 13.3          | 66.2 ± 13.6            | 68.6 ± 10.2  | 69.3 ± 12.1              | 0.006   |
| Male gender, n (%)                                | 598 (68.6%)          | 202 (73.5%)            | 158 (79.0%)  | 199 (59.6%)              | <0.001* |
| Body weight (kg)                                  | 60.3 ± 13.0          | 62.9 ± 13.4            | 62.8 ± 13.1  | 56.8 ± 12.0              | <0.001* |
| Body surface area (m <sup>2</sup> )               | 1.63 ± 0.21          | 1.67 ± 0.21            | 1.66 ± 0.19  | 1.57 ± 0.20              | <0.001* |
| Diabetes, n (%)                                   | 239 (27.4%)          | 27 (9.8%)              | 121 (60.5%)  | 83 (24.9%)               | <0.001‡ |
| Hypertension, n (%)                               | 464 (53.2%)          | 174 (63.3%)            | 119 (59.5%)  | 165 (49.4%)              | 0.002   |
| Hyperlipidemia, n (%)                             | 334 (38.3%)          | 86 (31.3%)             | 142 (71.0%)  | 99 (29.6%)               | <0.001† |
| CKD, n (%)  | 187 (21.4%)          | 48 (17.5%)             | 54 (27.0%)   | 78 (23.4%)               | 0.039   |
| Hemodialysis, n (%)                               | 56 (6.4%)            | 11 (4.0%)              | 16 (8.0%)    | 25 (7.5%)                | 0.13    |
| COPD, n (%)                                       | 34 (3.9%)            | 12 (4.4%)              | 5 (2.5%)     | 14 (4.2%)                | 0.52    |
| Currently smoking, n (%)                          | 47 (5.4%)            | 25 (9.1%)              | 12 (6.0%)    | 9 (2.7%)                 | 0.002   |
| Elective, n (%)                                   | 728 (83.5%)          | 218 (79.3%)            | 160 (80.0%)  | 306 (91.6%)              | <0.001* |
| Urgent, n (%)                                     | 92 (10.6%)           | 18 (6.5%)              | 35 (17.5%)   | 24 (7.2%)                | <0.001† |
| Emergency, n (%)                                  | 49 (5.6%)            | 35 (12.7%)             | 5 (2.5%)     | 4 (1.2%)                 | <0.001  |
| Hypothermia, n (%)                                | 128 (14.7%)          | 108 (39.3%)            | 2 (1.0%)     | 11 (3.3%)                | <0.001  |
| Preoperative SFL (mg/dL)                          | 331 ± 101            | 315 ± 112              | 357 ± 96     | 329 ± 92                 | <0.001† |
| Preoperative platelet count (10 <sup>3</sup> /μL) | 189 ± 69             | 183 ± 73               | 199 ± 68     | 183 ± 61                 | 0.014   |
| Perfusion time (min)                              | 192 ± 84             | 230 ± 91               | 153 ± 55     | 186 ± 79                 | <0.001‡ |
| Lowest core temperature (°C)                      | 30.9 ± 4.4           | 26.5 ± 4.1             | 33.5 ± 1.5   | 32.7 ± 2.4               | <0.001‡ |

CABG coronary artery bypass grafting, CKD chronic kidney disease, COPD chronic obstructive pulmonary disease

Statistically significant differences indicated as follows: \* $p < 0.001$  valvular surgery vs CABG, aortic surgery, † $p < 0.001$  CABG vs aortic surgery, valvular surgery, ‡ $p < 0.001$  among every procedure

committee for treating intraoperative coagulopathy due to hypofibrinogenemia.

This retrospective study was performed under a waiver of authorization approved by the institutional review board of Nagoya University School of Medicine, Aichi, Japan (2014–0026).

### Statistical analyses

Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as means  $\pm$  standard deviations. Differences between two groups were detected by a *t* test. A Chi-square test was used for categorical variables. Univariate comparisons were performed with an analysis of variance (ANOVA) for normally distributed data. Correlations among data were analyzed by determining Pearson's coefficients. A factor analysis was performed with a logistic regression analysis. All variables presented were tested in univariate analyses, and variables with *p* value  $< 0.10$  were entered into the multivariate regression models. A *p* value  $< 0.05$  was considered to be statistically significant. The receiver operating characteristic curve analysis was performed to identify the best preoperative SFL cutoff value to predict hypofibrinogenemia. As three comparisons were performed for each parameter at each procedure, the risk of obtaining significant results due to chance was increased. Bonferroni's adjustment was therefore applied: each *p* value was multiplied by the number of comparisons (i.e., 3 $\times$ ). These statistical analyses were performed with the JMP Pro version 13.0.0 software program (SAS Institute, Cary, NC, USA).

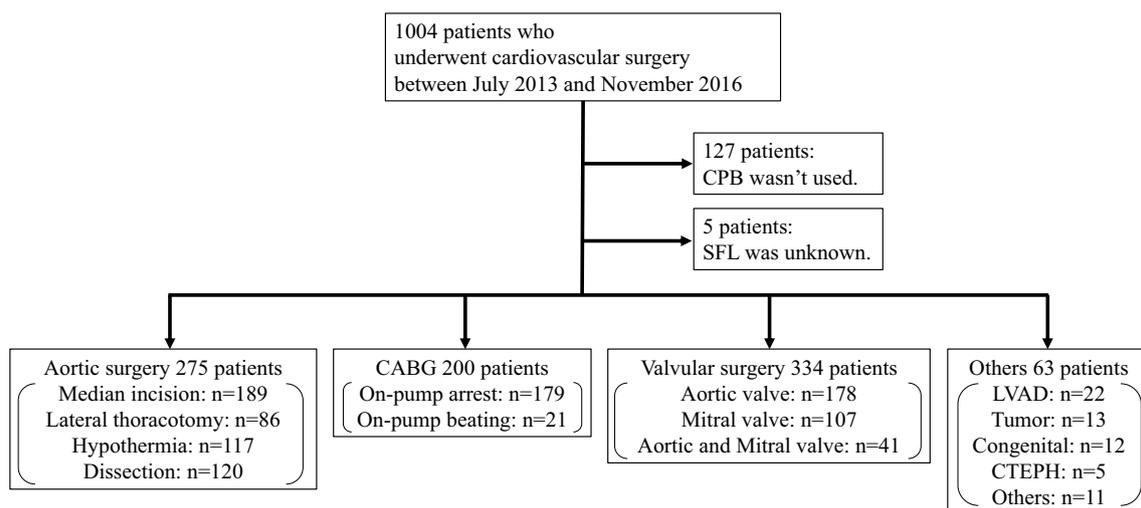
### Results

The mean age of the patients was  $66.9 \pm 13.3$  years. There were 49 patients who underwent emergency surgery and 92 who underwent urgent operations. The details of the surgical procedures were as follows: 275 patients underwent aortic surgery (189 median sternal incision, 86 left thoracotomy, 117 hypothermia and 120 aortic dissection), 200 patients underwent CABG (179 on-pump arrest and 21 on-pump beating), 334 cases underwent valvular surgery (178 aortic valve, 107 mitral valve, 41 aortic and mitral valves, and 8 others), and 63 patients underwent other surgeries (Fig. 1).

### Intraoperative lowest SFL

The average intraoperative lowest SFL of all cases, aortic surgery, CABG and valvular surgery was  $185 \pm 71$ ,  $156 \pm 65$ ,  $198 \pm 69$  and  $198 \pm 68$  mg/dL, respectively (Supplement Fig. 2–5). Aortic surgery had a significantly lower intraoperative lowest SFL than CABG ( $p < 0.001$ ) and valvular surgery ( $p < 0.001$ , Supplement Fig. 6). The incidence of hypofibrinogenemia  $\leq 150$  mg/dL was 32.8%, 50.2%, 26.5% and 22.8% in all cases, aortic surgery, CABG and valvular surgery, respectively.

In aortic surgery, the average preoperative SFL in elective degenerative aneurysm, acute dissection and chronic dissection was  $318 \pm 90$ ,  $294 \pm 150$  and  $285 \pm 92$  mg/dL, respectively. The average intraoperative SFL in elective degenerative aneurysm, acute dissection and chronic dissection was  $158 \pm 46$ ,  $152 \pm 95$  and  $140 \pm 54$  mg/dL, respectively. A one-way ANOVA showed no significant difference in the



**Fig. 1** Patient selection flowchart. CPB cardiopulmonary bypass, SFL serum fibrinogen level, CABG coronary artery bypass grafting, LVAD left ventricular assist device, CTEPH chronic thromboembolic pulmonary hypertension

preoperative SFL or intraoperative lowest SFL ( $p = 0.084$ ,  $p = 0.13$ , Supplement Fig. 7).

The average preoperative SFL in elective degenerative aneurysm, elective valvular surgery and elective CABG was  $318 \pm 90$ ,  $323 \pm 88$  and  $346 \pm 88$  mg/dL, respectively. Elective CABG had a significantly higher preoperative SFL than elective degenerative aneurysm ( $p = 0.006$ ) and elective valvular surgery ( $p = 0.007$ , Supplement Fig. 8). In addition, the average intraoperative SFL in elective degenerative aneurysm, elective valvular surgery and elective CABG was  $158 \pm 46$ ,  $195 \pm 63$  and  $188 \pm 58$  mg/dL, respectively. Elective degenerative aneurysm had a significantly lower intraoperative SFL than elective CABG ( $p < 0.001$ ) and elective valvular surgery ( $p < 0.001$ , Supplement Fig. 8).

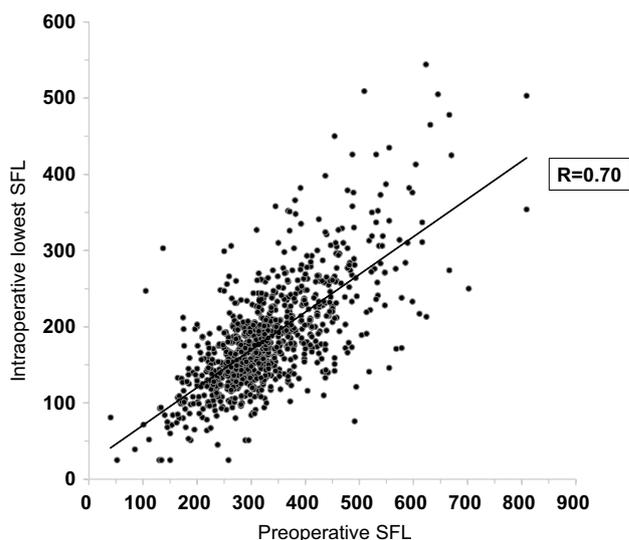
While not significant, the intraoperative lowest SFL in emergent aortic surgery was lower than that in elective surgery ( $146 \pm 82$  vs.  $154 \pm 55$  mg/dL,  $p = 0.47$ ). Although the incidence of hypofibrinogenemia  $\leq 150$  mg/dL of emergent aortic surgery was not significantly different from that of elective aortic surgery (62.9% vs. 50.5%,  $p = 0.20$ ), the incidence of severe hypofibrinogenemia  $\leq 100$  mg/dL of emergent aortic surgery was significantly higher than that of elective aortic surgery (34.3% vs. 12.8%,  $p = 0.004$ ). There was neither a significant difference in the intraoperative lowest SFL ( $156 \pm 69$  vs.  $157 \pm 54$  mg/dL,  $p = 0.94$ ) nor in the incidence of hypofibrinogenemia  $\leq 150$  mg/dL (51.3% vs. 50.0%,  $p = 0.90$ ) between median sternotomy and lateral thoracotomy. There was also no significant difference in the intraoperative lowest SFL ( $155 \pm 68$  vs.  $157 \pm 62$  mg/dL,  $p = 0.85$ ) or ratio of hypofibrinogenemia  $\leq 150$  mg/dL (54.7% vs. 48.1%,  $p = 0.33$ ) between hypothermia operation (lowest core temperature  $\leq 25$  °C) and others (lowest core temperature  $> 25$  °C).

In valvular surgery, although not significant, the intraoperative lowest SFL of re-do operation was lower than that of primary operation ( $192 \pm 86$  vs.  $200 \pm 63$  mg/dL,  $p = 0.45$ ). However, the incidence of hypofibrinogenemia  $\leq 150$  mg/dL in re-do valvular surgery was significantly higher than that in primary operation (36.5% vs. 19.6%,  $p = 0.007$ ).

### Predictors for hypofibrinogenemia

The intraoperative lowest SFL showed a strong correlation with the preoperative SFL values ( $r = 0.70$ , Fig. 2). However, they showed no correlation with the CPB time ( $r = -0.25$ ) or the lowest core temperature ( $r = 0.24$ ).

The predictors of hypofibrinogenemia  $\leq 150$  mg/dL were preoperative SFL (odds ratio 0.98; 95% confidence interval 0.98–0.99,  $p < 0.001$ ), re-do surgery (odds ratio 1.73; 95% confidence interval 1.10–2.72,  $p = 0.017$ ) and perfusion time (odds ratio 1.004; 95% confidence interval 1.002–1.007,  $p < 0.001$ ) as identified by a logistic regression analysis (Table 2).



**Fig. 2** The preoperative SFL and intraoperative lowest SFL showed a strong correlation. SFL serum fibrinogen level

**Table 2** Univariate and multivariate risk factor analyses for intraoperative hypofibrinogenemia (SFL  $\leq 150$  mg/dL)

| Parameters              | Univariate     | Multivariate   | OR (95% CI)         |
|-------------------------|----------------|----------------|---------------------|
|                         | <i>p</i> value | <i>p</i> value |                     |
| Preoperative SFL        | $< 0.001$      | $< 0.001$      | 0.98 (0.98–0.99)    |
| Body weight             | 0.83           |                |                     |
| Emergency operation     | 0.018          | 0.75           |                     |
| Re-do                   | $< 0.001$      | 0.017          | 1.73 (1.10–2.72)    |
| Aortic surgery          | $< 0.001$      | 0.38           |                     |
| Left lateral incision   | $< 0.001$      | 0.31           |                     |
| Aortic dissection       | $< 0.001$      | 0.25           |                     |
| TAAA                    | 0.004          | 0.12           |                     |
| Lowest core temperature | $< 0.001$      | 0.27           |                     |
| Perfusion time          | $< 0.001$      | $< 0.001$      | 1.004 (1.002–1.007) |

OR odds ratio, CI confidence interval, SFL serum fibrinogen level, TAAA thoracoabdominal aortic aneurysm

Using the receiver operating characteristics curve analysis, we found that the best preoperative SFL cutoff value for predicting hypofibrinogenemia  $\leq 150$  mg/dL was 308.5 mg/dL (Supplement Fig. 9). The area under the curve for preoperative SFL was 0.81 (95% confidence interval 0.78–0.84). For convenience, assuming a preoperative SFL 300 mg/dL as the cutoff value, the odds ratio for hypofibrinogenemia was found to be 7.22 (95% confidence interval 5.26–9.92,  $p < 0.001$ ). Using this cutoff value, the sensitivity, specificity, positive predictive value and negative predictive value were 72.4%, 73.4%, 57.0% and 84.5%, respectively.

We compared the incidence of hypofibrinogenemia in aortic surgery with that in other surgeries by the preoperative SFL (Supplement Table 1). For any preoperative SFL, the incidence of hypofibrinogenemia in aortic surgery was higher than that in other surgeries. The lower the preoperative SFL, the higher the incidence of hypofibrinogenemia in both aortic surgery and other surgeries.

### Platelet counts

We focused on the SFL in this study, but the platelet count is also important in cardiovascular surgery. A one-way ANOVA showed a significant difference in the preoperative platelet count among the three groups ( $p=0.014$ ). The preoperative platelet counts in CABG ( $199 \times 10^3/\mu\text{L}$ ) were significantly higher than in aortic surgery ( $183 \times 10^3/\mu\text{L}$ ,  $p=0.016$ ) and valvular surgery ( $183 \times 10^3/\mu\text{L}$ ,  $p=0.005$ ). Furthermore, a one-way ANOVA showed significant difference in the postoperative platelet count among the three groups as well ( $p=0.002$ ). The postoperative platelet counts in CABG ( $107 \times 10^3/\mu\text{L}$ ) were significantly higher than in valvular surgery ( $96 \times 10^3/\mu\text{L}$ ,  $p<0.001$ ), and while not significant, the counts were higher than in aortic surgery as well ( $101 \times 10^3/\mu\text{L}$ ,  $p=0.0501$ ). The reason for the high preoperative platelet count in CABG is unknown. Intraoperative platelet consumption is thought to be high in aortic surgery, but the postoperative platelet count is thought to be around  $100 \times 10^3/\mu\text{L}$  in all groups because of PC transfusion.

### Preoperative medication (antiplatelet or anticoagulation drugs)

A one-way ANOVA showed significant differences in preoperative medication, such as antiplatelet or anticoagulation drugs, among the three groups ( $p<0.001$ , Supplement Table 2). CABG (19.5%) cases were most likely to have received any anticoagulant or antiplatelet drug within 5 days before surgery, followed by aortic surgery (6.9%,  $p<0.001$ ) and valvular surgery (6.3%,  $p<0.001$ ).

### Usage of tranexamic acid and fibrinogen concentrate

Tranexamic acid and fibrinogen concentrates are important drugs that affect the coagulation system. A one-way ANOVA showed a significant difference in the dose of tranexamic acid among the three groups (CABG  $894.5 \pm 921.7$  units, aortic surgery:  $1167.6 \pm 1049.3$  units, valvular surgery:  $1133.2 \pm 955.8$  units,  $p<0.001$ ; Supplement Table 3). The rate of administration was 59.0% in CABG, 68.7% in aortic surgery and 69.2% in valvular surgery, showing no significant differences among the three groups ( $p=0.32$ ). Fibrinogen concentrate was administered at a significantly higher

dose and rate in aortic surgery ( $3.2 \pm 3.3$  g, 67.6%) than in CABG ( $0.6 \pm 1.6$  g, 16.5%) and valvular surgery ( $0.8 \pm 2.0$  g, 21.6%).

## Discussion

In this study, we examined the intraoperative SFL and incidence of hypofibrinogenemia in aortic surgery, CABG and valvular surgery and identified the risk factors of hypofibrinogenemia. Half of aortic surgery cases showed hypofibrinogenemia, while only 20% of CABG or valvular surgery cases showed hypofibrinogenemia. We identified the preoperative SFL, re-do surgery and perfusion time as risk factors for hypofibrinogenemia.

A previous trial independently described the perioperative SFL in CABG and aortic surgery [1–8]. In the present study, the lowest intraoperative SFL values were described for aortic surgery, CABG and valvular surgery. A prospective observational trial showed that the preoperative SFL was independently associated with excessive bleeding after cardiac operations [9]. The present study is the first to show that the preoperative SFL is associated with intraoperative hypofibrinogenemia.

The incidence of hypofibrinogenemia in aortic surgery is higher than that in valvular surgery and CABG. This is because most aortic surgeries, such as aortic arch surgery, require hypothermia for brain protection due to the long duration of CPB. Surgery for thoracoabdominal aorta is performed via a large spiral incision, which creates a large, invasive surgical field and is associated with the consumption of coagulation factors. Hypothermia, long-duration CPB and a large, invasive surgical field are associated with the consumption of coagulation factors and dysfunction of the coagulation system, which may lead to intraoperative coagulopathy.

Assuming that the circulating blood volume of the patient is 7% of the body weight, patients with a body weight of 60 kg have a circulating blood volume of 4200 mL. Hemodilution at the start of CPB occurs due to the filling fluid used for extracorporeal circulation and infusion at the time of anesthesia induction. In our institute, the priming volume for extracorporeal circulation is 1100 mL (Ringer's bicarbonate 800 mL and mannitol 300 mL) for a standard body size.

The infusion volume for induction of anesthesia differs among cases but is estimated to be approximately 1000 mL. Thus, the ratio of hemodilution at the start of CPB is approximately 0.67 ( $=4200/[4200 + 1100 + 1000]$ ). In aortic surgery requiring cerebral protection, the priming volume for the brain protection circuit should also be set at 150 mL. A setting of 150 mL increases the circulating blood volume and also positively contributes to hemodilution.

Smaller bodies are thought to have a lower circulating blood volume and therefore experience greater dilution by the circuit filling solution. The body surface area and body weight did not differ markedly between aortic surgery and CABG, but those values in the valvular surgery patients were significantly smaller than in others. However, since the priming volume for extracorporeal circulation was reduced to 800 mL (Ringer's bicarbonate 500 mL + mannitol 300 mL), in cases with a body surface area < 1.4, the difference in the degree of dilution due to body size was not expected to be substantial. For example, a patient with a body weight of 45 kg has a circulating blood volume of 3150 mL and the infusion volume for induction of anesthesia is estimated to be approximately 700 mL. Therefore, the ratio of hemodilution at the start of CPB is approximately 0.68 ( $=3150/[3150 + 800 + 700]$ ). It is almost same as a patient with a body weight of 60 kg as above mentioned.

The preoperative SFL in aortic surgery was not markedly different from that in valvular surgery, while the preoperative SFL in CABG was significantly higher than that in others (Table 1). In case of aortic dissection, fibrinogen is known to be consumed due to thrombus formation in the false lumen.

The perfusion time was longest in aortic surgery, followed by valvular surgery and CABG. In a multivariate analysis, the perfusion time was identified as a risk factor for hypofibrinogenemia. Coagulation factors are well known to be consumed in the extracorporeal circulation circuit. It is reasonable that a long perfusion time is a risk factor for hypofibrinogenemia.

The minimum body temperature was lowest in aortic surgery, followed by valvular surgery and CABG. Similar to the CPB duration, the minimum body temperature was also not identified as a risk factor for hypofibrinogenemia in a multivariate analysis in the present study. While hypothermic surgery is known to lead to dysfunction of coagulation factors and platelets, hypothermic surgery is not believed to directly affect the intraoperative lowest SFL based on the present findings.

In aortic surgery, hypofibrinogenemia occurs at a higher rate in patients with a preoperative SFL  $\leq 300$  mg/dL than in others, being particularly frequent in patients with preoperative SFL  $\leq 250$  mg/dL (Supplement Table 1). Because hypofibrinogenemia is a major causative factor of coagulopathy, the importance of fibrinogen supplementation has been mentioned [10, 11]. It is therefore essential to prepare FFP, fibrinogen concentrate or cryoprecipitate for coagulation factor supplementation. The amount of fibrinogen contained in FFP is not large. To improve the coagulation under hypofibrinogenemia, a large volume of FFP transfusion would be necessary; furthermore, it takes a longer time for a full recovery of the SFL to be achieved after the administration of FFP. In comparison, fibrinogen concentrate and cryoprecipitate include large amounts of

fibrinogen per volume and can efficiently replenish the SFL [11]. In patients with a preoperative SFL  $\leq 250$  mg/dL, especially those who are likely to develop hypofibrinogenemia, the administration of fibrinogen concentrate or cryoprecipitate is effective. In cardiac surgery, some studies have demonstrated the effectiveness of the prophylactic administration of fibrinogen concentrate [12, 13], although most have evaluated its therapeutic administration against coagulopathy after the termination of CPB [6, 14–20]. In cardiovascular surgery, the effect of fibrinogen on improving the survival rate is unclear, but evidence has shown that it reduces the hemorrhage volume and erythrocyte transfusion volume [20]. Because patients undergoing cardiovascular surgery are at a high risk for developing thrombosis, physicians should be alert for thrombotic adverse events due to the administration of coagulation factor concentrates [21]. However, the administration of fibrinogen concentrate does not itself increase the incidence of thromboembolism, and it has been shown to be an extremely safe blood product [20, 22]. At present, fibrinogen concentrate is not approved for use in the treatment of intraoperative hypofibrinogenemia under the Japanese health insurance system, and we use it under institutional approval. Fibrinogen concentrate is used in 68% of aortic surgery cases. Allergy has not been recognized, and the rate of embolism has not increased. In addition, it was confirmed that the SFL increased promptly upon the administration of fibrinogen concentrate [7].

We focused on SFL in this study, but the platelet count is also important. A reduced platelet count is associated with adverse clinical outcomes in type A acute aortic dissection. A recent retrospective study reported that increasing age, male gender, lower serum levels of TFPI, higher serum levels of FDP and a shorter attack time were significantly associated with lower platelet counts at admission [23]. Therefore, in the perioperative period, not only the SFL but also the platelet count should be observed.

Several limitations associated with the present study warrant mention. First, although the number of cases in this study was large, the background characteristics of the cases differed. For example, in aortic surgery, the replacement range differed among cases. In CABG, the number of grafts also differed among cases, and in valvular surgery, the number of valves differed. Second, this was a retrospective study, and confounders were not completely excluded. Third, this study was based on data from a single institution only. Fourth, the surgeon and anesthesiologist differed among cases.

## Conclusion

The incidence of hypofibrinogenemia in aortic surgery was high, and half of aortic surgery cases showed an SFL  $\leq 150$  mg/dL. The preoperative SFL, re-do surgery and

perfusion time aortic surgery were identified as predictors of hypofibrinogenemia. A preoperative SFL of 300 mg/dL was determined to be the cutoff value by an ROC curve analysis. The intraoperative measurement of SFL is important for detecting hypofibrinogenemia and applying appropriate and prompt transfusion treatment.

## Compliance with ethical standards

**Conflict of interest** The authors have declared that no conflict of interest exists.

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