Submitted: 03 January, 2023 Accepted: 14 February, 2023 Published: 08 November, 2023 DOI:10.22514/sv.2023.072

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ORIGINAL RESEARCH

Evaluation of fibrinogen function by CFF-A10 in cardiac surgery

Minako Furuta[1], Hisakatsu Ito[2,*], Shota Sakai[2], Daisuke Hibi[2], Mitsuaki Yamazaki[3]

[1]Department of Anesthesiology, Toyama Prefectural Central Hospital, 930-8550 Toyama, Japan
[2]Department of Anesthesiology, Toyama University Hospital, 930-0194 Toyama, Japan
[3]Department of Anesthesiology, Toyama Nishi General Hospital, 939-2716 Toyama, Japan

***Correspondence**
hisa@med.u-toyama.ac.jp
(Hisakatsu Ito)

Abstract

Fibrinogen function is evaluated as the maximum amplitude (MA) of the citrated functional fibrinogen (CFF) assay in TEG6s®, however, CFF-MA requires a long time to obtain results. CFF-A10 (10-minute value), allowing more rapid decisions, however, no studies have evaluated the correlation between CFF-A10 levels and fibrinogen concentration. This study aimed to assess the correlation between CFF-A10 and blood fibrinogen levels measured using the dry hematology method after cardiopulmonary bypass (CPB). This retrospective study was conducted in a single university hospital and enrolled 192 patients of all ages who underwent cardiovascular surgery with CPB between 01 March 2020, and 05 November 2021. CFF-A10 and CFF-MA levels were measured using the TEG6s® global hemostasis assay, and blood fibrinogen levels were measured using the Fibcare® DRIHEMATO Fib-HSII after CPB. Simple linear regression analysis was used to evaluate the relationship between TEG6s® parameters and fibrinogen concentration. Furthermore, the patients were classified into four groups based on the cut-off values of fibrinogen at 150 mg/dL and CFF-A10, and the background factors for each group were analyzed. CFF-A10 and blood fibrinogen levels were correlated by linear regression ($p < 0.0001$, $R^2 = 0.37$), similar to CFF-MA and fibrinogen levels ($p < 0.0001$, $R^2 = 0.40$). The optimal cut-off value, which maximizes the sensitivity and specificity, of CFF-A10 for predicting low fibrinogen levels below 150 mg/dL, was 8.4 mm, with a sensitivity of 80.7% and specificity of 67.9%; that of CFF-MA was 9.2 mm, with a sensitivity of 76.3% and specificity of 69.8%. Despite sufficient blood fibrinogen levels, patients with low CFF-A10 levels experienced more postoperative bleeding. CFF-A10 predicted fibrinogen loss faster and with the same accuracy as CFF-MA did. Low CFF-A10 levels, despite sufficient fibrinogen levels, may be associated with increased blood loss following CPB.

Keywords

CFF-A10; CFF-MA; Fibrinogen; Hemostasis; Thromboelastometory

1. Introduction

Fibrinogen is a critical substrate for hemostasis involved in both primary and secondary hemostasis [1–4]; the strength of blood clots is dependent on the fibrinogen concentration [5]. Certain fibrinogen concentrations are necessary for optimal hemostasis to avoid large-volume transfusion during cardiac surgery with cardiopulmonary bypass (CPB) [6]. Guidelines recommend fibrinogen supplementation with cryoprecipitate or fibrinogen concentrate for fibrinogen loss to reduce the requirement for transfusions in cardiac surgery for adults, children, and neonates [7–10]. Therefore, the necessity for supplementation of fibrinogen concentration must be assessed by identifying a decrease in fibrinogen concentration or function.

Viscoelastic hemostatic assays should be incorporated into the transfusion algorithm during cardiac surgery so that rapid blood management decisions can be taken when needed [7–11]. TEG6s® (Haemonetics, Braintree, MA, USA) is a cartridge-based automated device that measures clot viscoelasticity in whole blood using the resonance method. The maximum amplitude of the citrated functional fibrinogen (CFF-MA) was used to evaluate the contribution of fibrinogen to clot strength using TEG6s® [12]. However, CFF-MA requires a long time to obtain results, particularly when the clot strength is low. Therefore, CFF-MA often does not fulfill its role as a point-of-care monitor for rapid results. Meanwhile, a recently installed parameter called CFF-A10 shows the level of clot strength 10 min after the start of the test, allowing more rapid decisions to manage blood coagulation. However, no studies have evaluated the correlation between CFF-A10 levels and fibrinogen concentration. In the present study, we analyzed the correlation between CFF-A10 and blood fibrinogen levels. Furthermore, we classified the patients

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into four groups based on the cutoff values of fibrinogen and CFF-A10 and then sub-analyzed the background factors for each group.

2. Materials and methods

Study design and participants: For this retrospective, single-center study, patients were recruited from 01 March 2020, to 05 November 2021, at Toyama University Hospital. Patients including all ages who underwent cardiovascular surgery with CPB were included in this study. All eligible patients were given the opportunity to opt out.

Data collection: Baseline characteristics of the patients (age, sex, body surface area (Du Bois Method), and preoperative laboratory findings), intraoperative (post-protamine) TEG6s® parameters, blood fibrinogen levels, and blood count data were collected. We also collected data on the diagnoses and surgical procedures, anesthetic time, operating time, aortic clamp time, intraoperative fluid volume, intraoperative transfusion volume (red cell concentration, fresh frozen plasma, platelet concentration, fibrinogen), intraoperative blood loss, blood loss in the intensive care unit (ICU), and transfusion volume in the ICU.

Perioperative management of anesthesia: All patients received routine general cardiac anesthesia. An initial dose of heparin (400 units/kg) was administered prior to CPB, with additional heparin as needed to exceed 480 s of activated clotting time (ACT) (Actalyke MINI II, Helena Laboratories, USA). After weaning from CPB, protamine was administered to reverse the heparin dose. After 3 min of protamine administration, blood was collected *via* an artery catheter, and ACT, TEG6s®, blood fibrinogen levels, and blood count were measured. Blood fibrinogen levels were assessed using the dry hematology method with a Fibcare® DRIHEMATO Fib-HSII (Atom Medical Corp., Tokyo, Japan). Perioperative blood transfusion was performed at the clinician's discretion and guided by the results of TEG6s® and fibrinogen concentrations.

CFF-A10 and MA: We performed a TEG6s® global hemostasis assay after CPB using citrated blood. The CFF channel, which uses tissue factors as coagulation activators and Glycoprotein IIb/IIIa inhibitors to neutralize platelet function, shows the contribution of fibrinogen to clot strength. CFF-A10 shows the clot strength in the CFF channel 10 min after starting the test. CFF-MA shows the maximum amplitude of the clot strength in CFF.

Statistical analysis Simple linear regression was performed to evaluate the relationship between CFF-A10 and blood fibrinogen levels. Receiver operating characteristic (ROC) curves were constructed. The cut-off values of CFF-A10 were calculated to predict a fibrinogen concentration of 150 mg/dL with the best sensitivity and specificity using Youden's index. The patients were classified into four groups based on 150 mg/dL of fibrinogen levels and CFF-A10 values (Group A fibrinogen level $\geq$150 mg/dL and CFF-A10 $\geq$8.4; Group B: fibrinogen level $\geq$150 mg/dL and CFF-A10 $<$8.4; Group C: fibrinogen level $<$150 mg/dL and CFF-A10 $<$8.4; and group D: fibrinogen level $<$150 mg/dL and CFF-A10 $\geq$8.4). They were compared in terms of background factors, intraoperative and postoperative blood transfusion volumes, and postoperative blood loss. Postoperative blood loss was defined as the amount of blood in the drainage tube from the time of admission to the ICU until ICU discharge or removal of the drainage tube. Data are expressed as mean $\pm$ SD. The statistical significance of differences between the groups was evaluated with one-way or two-way repeated measures Analysis of Variance (ANOVA) followed by the Bonferroni multiple comparisons test, as appropriate. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using GraphPad Prism software version 9.3.1 for Windows (GraphPad Software, San Diego, California, USA).

3. Results

A total of 192 patients were enrolled in this study. Twenty-five patients were excluded because of missing data, the postoperative introduction of extracorporeal membrane oxygenation, or other reasons (Fig. 1). Baseline clinical and laboratory characteristics of the study population are shown in Table 1.

Fibrinogen and CFF-A10 showed a significant linear correlation ($p < 0.0001$, $R^2 = 0.37$), similar to that of fibrinogen and CFF-MA ($p < 0.0001$, $R^2 = 0.40$) (Fig. 2). The ROC curve analysis showed that the cut-off value of CFF-A10 for predicting a fibrinogen concentration of 150 mg/dL was 8.4 mm, with a sensitivity of 80.7% and specificity of 67.9%; that of CFF-MA was 9.2 mm, with a sensitivity of 76.3% and specificity of 69.8% (Fig. 3).

Based on their fibrinogen levels and CFF-A10. A comparison of the backgrounds of the four groups showed that patients in group B (with low CFF-10 levels despite sufficient blood fibrinogen levels), were significantly younger and tended to be younger than one year (Table 1). There were significantly more patients with cyanotic congenital heart disease in Group B than in the other groups. There were also no significant differences among the four groups in terms of anesthesia, operation, CPB, and aortic clamp times.

There were no significant differences in the reaction times of citrated kaolin activated intrinsic pathway assay (CK-R) and citrated kaolin activated intrinsic pathway assay with heparinase (CKH-R) among the four groups. Citrated rapid TEG assay-maximum amplitude (CRT-MA) levels were low in groups B and C (Table 2). The intraoperative fibrinogen dose was significantly higher in Group C than in the other groups. There were also no significant differences in the amount of intraoperative blood loss or transfusion between the groups (Table 3). Postoperative blood loss was significantly higher in Group B than in Group C (Fig. 4).

Re-analysis of linear regression excluding patients under 1 year of age showed a higher association between fibrinogen and CFF-A10 ($p < 0.0001$, $R^2 = 0.40$), and MA ($p < 0.0001$, $R^2 = 0.43$), as well as higher sensitivity and specificity (sensitivity of 82.6% and specificity of 71.4% in CFF-A10, and sensitivity of 79.4% and specificity of 71.4% in CFF-MA) with ROC analysis (**Supplementary Fig. 1**). In a comparison of the four groups without infant, group B was still significantly younger. Preoperative fibrinogen levels were significantly higher in group A (**Supplementary Table 1**).

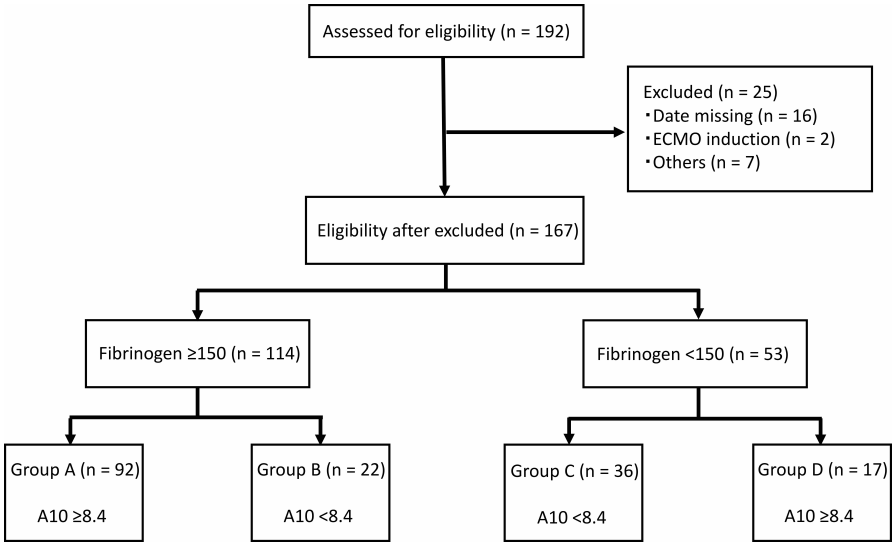

FIGURE 1. Flow diagram of this study. A total of 192 patients were enrolled in this study, and 25 patients were excluded due to missing data, the postoperative introduction of extracorporeal membrane oxygenation, or other reasons. ECMO: extracorporeal membrane oxygenation.

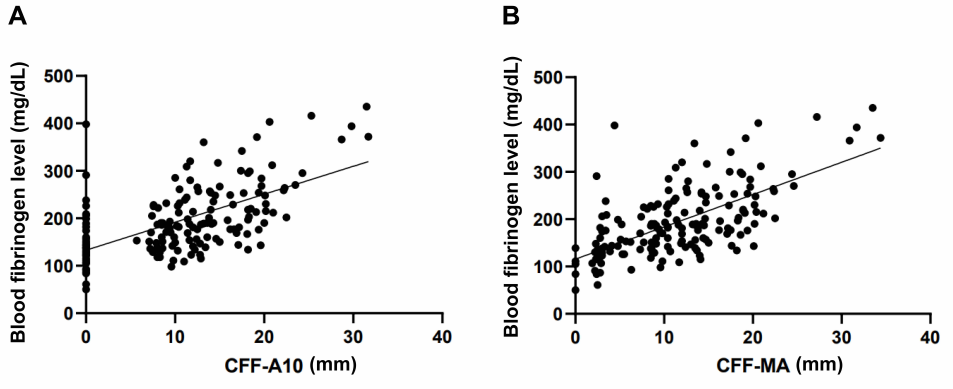

FIGURE 2. Relationship between CFF-A10 (A) or CFF-MA (B) and the level of blood fibrinogen. There were significant linear correlations between fibrinogen and CFF-A10 (A; $p < 0.0001$, $Y = 5.9 \times X + 132.9$, $R^2 = 0.37$), and between fibrinogen and CFF-MA (B; $p < 0.0001$, $Y = 6.8 \times X + 115.5$, $R^2 = 0.40$). CFF-A10: citrated functional fibrinogen-10-minute value; CFF-MA: citrated functional fibrinogen -maximum amplitude.

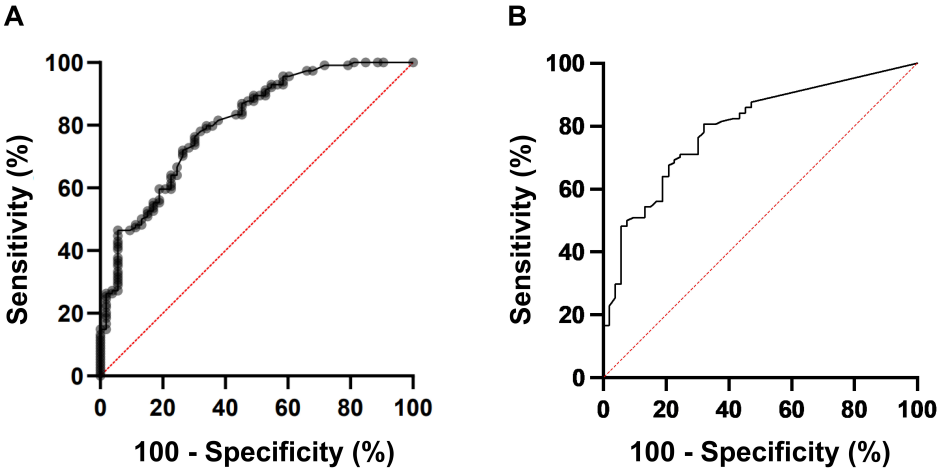

FIGURE 3. The ROC curve to detect fibrinogen concentration below 150 mg/dL in CFF-A10 and MA. The optimal cut-off was calculated to maximizes sensitivity and specificity. The cut-off value of CFF-A10 for predicting a fibrinogen concentration of 150 mg/dL was 8.4 mm, with a sensitivity of 80.7% and specificity of 67.9% (A). On the other hand, that of CFF-MA was 9.2 mm, with a sensitivity of 76.3% and specificity of 69.8% (B).

TABLE 1. Clinical and laboratory characteristic of the patients in group A, B, C, and D.

Variable	All (n = 167)	Group A	Group B	Group C	Group D	*p*-value
Number of patients (all ages), no. (%)	167	92 (55%)	22 (13%)	36 (22%)	17 (10%)	-
Age, mean ± SD (yr)	44.4 ± 32.7	48.4 ± 33.0	20.9 ± 28.2[a]	42.1 ± 29.1	59.3 ± 28.0[b]	0.012
Younger than one year (%)	27 (16%)	17 (18%)	6 (27%)	1 (3%)	3 (17%)	0.07
BSA (m^2)	1.24 ± 0.59	1.25 ± 0.59	0.89 ± 0.63	1.36 ± 0.48[b]	1.37 ± 0.56	0.02
Performed surgeries						
Cyanotic congenital heart disease	40	17	9[a]	3[b]	2	0.04
One valve repair	64	33	4	16	11[a,b]	0.01
Two or more valves repair	7	6	0	0	1	0.27
VSD or ASD repair	17	9	4	3	1	0.57
Thoracic aorta replacement	25	14	2	7	2	0.73
Left ventricular assist device	4	4	0	0	0	0.34
Coronary artery bypass graft	5	4	1	0	0	0.49
Other	5	5	2	7[a]	0	0.04
CPB						
Bypass time ± SD	179.1 ± 73.50	177.6 ± 70.79	194.5 ± 71.86	177.4 ± 82.71	169.1 ± 71.21	0.72
Aortic clamp time ± SD	105.4 ± 57.10	105.7 ± 54.01	111.0 ± 56.51	112.8 ± 55.03	112.4 ± 51.01	0.90
Operation time ± SD	310.1 ± 135.8	304.3 ± 142.0	344.6 ± 116.1	917.5 ± 141.6	276.6 ± 106.4	0.43
Anesthesia time ± SD	389.3 ± 147.9	383.2 ± 153.5	434.3 ± 125.2	398.0 ± 154.0	340.5 ± 117.7	0.24
Serum creatinine, mean ± SD (mg/dL)	0.940 ± 1.24	1.105 ± 1.71	0.503 ± 0.29	0.897 ± 1.29	0.754 ± 0.31	0.30
Preoperative hemoglobin, mean, ± SD (mg/dL)	13.21 ± 2.04	12.87 ± 2.05	13.89 ± 1.77	13.77 ± 1.99	12.95 ± 2.11	0.03
Preoperative platelet count, mean, ± SD ($\times 10^3/\mu L$)	22.96 ± 10.99	23.62 ± 12.07	26.80 ± 9.48	21.53 ± 8.77	17.41 ± 8.77	0.01
PT-INR, mean ± SD	1.065 ± 0.25	1.076 ± 0.26	0.994 ± 0.13	1.014 ± 0.21	1.203 ± 0.34	0.08
APTT, mean ± SD (s)	34.19 ± 7.74	35.81 ± 9.07	30.70 ± 3.17[a]	31.35 ± 4.05[a]	35.88 ± 7.18	<0.0001
Blood fibrinogen level, mean ± SD (mg/dL)	302.3 ± 118.30	345.2 ± 137.60	234.6 ± 63.27[a]	256.2 ± 64.60[a]	268.6 ± 44.63	<0.0001

The data are represented as number (percentage) or mean ± standard deviation, as appropriate.
a: The results of Bonferroni's multiple comparisons test for multiple comparisons or Fisher's exact test: $p < 0.05$, versus Group A.
b: Results of Bonferroni's multiple comparisons test for multiple comparisons or Fisher's exact test: $p < 0.05$, versus Group B.
Abbreviations: SD, standard deviation; BSA, body surface area; VSD, ventricular septal defect; ASD, articular septal defect; CPB, cardiopulmonary bypass; APTT, activated partial thromboplastin time; PT-INR, prothrombin time; and international normalized ratio.

TABLE 2. TEG parameters in group A, B, C and D.

TEG parameters	Group A	Group B	Group C	Group D	*p*-value
CK-R time, mean ± SD (min)	11.23 ± 4.5	9.95 ± 3.0	11.53 ± 4.4	10.60 ± 3.5	0.50
CKH-R time, mean ± SD (min)	10.5 ± 4.1	9.6 ± 2.8	10.7 ± 3.3	9.9 ± 2.6	0.64
CRT-MA, mean ± SD (mm)	50.8 ± 7.3	39.2 ± 5.3	37.7 ± 6.5	46.3 ± 7.5	<0.0001
CFF-A10, mean ± SD (mm)	15.5 ± 5.3	2.7 ± 3.6	1.8 ± 3.3	12.5 ± 3.1	<0.0001
CFF-MA, mean ± SD (mm)	15.9 ± 5.6	5.5 ± 2.3	3.9 ± 2.9	13.1 ± 3.2	<0.0001

The data represented as the mean ± standard deviation.
Abbreviations: TEG, thromboelastography; CK, citrated kaolin activated intrinsic pathway assay; CKH, citrated kaolin activated intrinsic pathway assay with heparinase; CRT, citrated rapid TEG assay; CFF, citrated functional fibrinogen; R time, reaction time; MA, maximum amplitude; A10, clot amplitude at 10 min.

The intraoperative fibrinogen dose was higher in group C (**Supplementary Table 1**). There were no other differences in intraoperative transfusion volume, blood loss, or operative time (data were not shown). Postoperative blood loss was tended to be high in Group B, but there was no difference (**Supplementary Fig. 2**).

4. Discussion

We showed that CFF-A10 correlated adequately with fibrinogen concentration by linear regression and accurately detected fibrinogen levels below 150 mg/dL through ROC curves, similar to CFF-MA. These results indicate that no clinically useful information can be obtained by waiting >10 min. Because coagulopathy contributes to bleeding, which further reduces coagulation factors and forms a vicious cycle; hence, quick decisions are required. Therefore, CFF-A10 is a useful parameter in clinical practice because it provides results faster than CFF-MA, but with the same accuracy. Erdoes *et al.* [13] reported a small prospective study, including twenty-three cardiac surgery patients who underwent functional fibrinogen assay using TEG6s® and rotational thromboelastometry (ROTEM). The correlations of TEG6s® system with standard coagulation parameters levels were quite similar to those of ROTEM and CFF-MA was good diagnostic accuracy for fibrinogen levels, however the test accuracy in CFF-A10 was not validate.

In the scatter plot of the relationship between CFF-A10 and fibrinogen concentration, there were a certain number of cases in which CFF-A10 was low or below the measurable limit despite the sufficient fibrinogen concentration measured by dry hematology. We presume that these cases decreased the accuracy of the test, particularly its specificity. Therefore, we classified the patients into four groups according to fibrinogen concentration and CFF-A10 value based on the cut-off value calculated from the ROC analysis because we thought it might affect the timing of the initiation of fibrinogen replacement therapy. In group B, with sufficient fibrinogen levels but low CFF-A10 levels, the postoperative blood loss increased in the ICU. Intraoperative blood loss was not significantly different between Group B and the other groups, suggesting that appropriate surgical hemostasis was performed as in the other groups. Based on these results, we hypothesized that postoperative blood loss in Group B was influenced by coagulopathy. The strength of blood clots is defined by the polymerization of platelets and fibrin. TEG6s® evaluate the strength of blood clots by fibrin polymerization in the CFF channel because platelet function is inhibited by the addition of integrin receptor antagonists. Fibrin polymerization was impaired in group B despite the presence of sufficient fibrinogen. A few adult cases also showed discrepancies between the clot strength and fibrinogen concentration. Kawashima *et al.* [14] classified only adult patients into four groups, which were divided by fibrinogen concentration and function using ROTEM, similar to our study. They also indicated that the group with sufficient fibrinogen levels, but low fibrinogen function in ROTEM, showed a significant increase in postoperative bleeding. Our results could support their report, which suggested that a vulnerable fibrin network or hyperfibrinolytic state could cause impaired fibrin polymerization, even in adults.

Group B was significantly younger and tended to be younger than one year. Previous studies have indicated the presence of neonatal fibrinogen, which could be fragile and not polymerized well, resulting in a vulnerable fibrin network despite adequate fibrinogen levels [15, 16]. Immature fibrinogen and fibrin net vulnerability could have caused coagulopathy in Group B. Furthermore, there were significantly more patients with cyanotic congenital heart disease in Group B. This result supports a previous study, which reported that in patients with cyanotic heart disease, the function of fibrinogen in clot formation is lower [17]. In infants with cyanotic congenital heart disease, the synthesis and metabolism of coagulation factors are often impaired because of hepatic dysfunction, which is a consequence of systemic hypoperfusion, hypoxemia, and hyperviscous blood perfusion [18]. However, there are no reports that have clarified the relationship between immature neonatal fibrinogen and cyanotic congenital heart disease. Some neonates with cyanotic disease in this study showed sufficient clot strength. Therefore, these factors cannot explain the cause of the discrepancy between the clot strength and fibrinogen concentration. Further studies specific to patients with cyanotic heart diseases are required.

This study has several limitations. First, it was a retrospective, single-center study with small sample size. Second, it

TABLE 3. The blood loss and the intraoperative and postoperative transfusion data.

Variables	All (n = 167)	Group A	Group B	Group C	Group D	*p*-value
Intraoperative blood loss (mL/BSA)	314.2 ± 567.8	327.6 ± 693.8	192.6 ± 118.9	321.8 ± 316.0	381.6 ± 577.4	0.05
Total intraoperative transfusion (mL/BSA)	684.5 ± 1017.0	721.0 ± 1151.0	518.3 ± 371.9	603.5 ± 710.8	871.3 ± 1339.0	0.63
Intraoperative red cell transfusion (mL/BSA)	281.9 ± 450.8	304.4 ± 501.9	226.2 ± 183.3	235.5 ± 338.1	329.6 ± 603.7	0.77
Intraoperative fresh frozen plasma transfusion (mL/BSA)	244.7 ± 332.5	262.4 ± 374.9	217.5 ± 180.9	190.6 ± 221.4	297.1 ± 428.1	0.62
Intraoperative platelet transfusion (mL/BSA)	86.5 ± 134.7	95.9 ± 133.9	28.9 ± 60.5	78.0 ± 119.1	127.2 ± 205.6	0.10
Intraoperative fibrinogen transfusion (g/BSA)	0.46 ± 0.84	0.22 ± 0.67	0.32 ± 0.65	1.14 ± 0.98[a,b]	0.55 ± 0.82	<0.0001
Postoperative blood loss (mL/BSA)	662.9 ± 877.7	632.7 ± 680.4	1107.0 ± 1724.0	449.4 ± 424.7[b]	705.7 ± 837.6	0.04
Total transfusion in ICU (mL/BSA)	512.2 ± 736.5	561.8 ± 823.1	557.3 ± 793.9	317.4 ± 398.7	595.6 ± 693.5	0.35
Red cell transfusion in ICU (mL/BSA)	224.9 ± 347.1	265.2 ± 420.5	195.3 ± 242.2	138.0 ± 179.9	226.2 ± 256.6	0.30
Fresh frozen plasma transfusion in ICU (mL/BSA)	250.8 ± 389.9	269.8 ± 418.0	264.6 ± 427.9	158.0 ± 238.2	326.2 ± 435.3	0.40
Platelet transfusion in ICU (mL/BSA)	36.55 ± 128.9	26.80 ± 92.2	97.43 ± 256.9	21.38 ± 68.5	43.25 ± 145.9	0.11

The data are represented as number (percentage) or mean ± standard deviation, as appropriate.
a: The results of Bonferroni's multiple comparisons test for multiple comparisons: $p < 0.05$, versus Group A.
b: Results of Bonferroni's multiple comparisons test for multiple comparisons: $p < 0.05$, versus Group B.
Abbreviations: BSA, body surface area; ICU, intensive care unit.

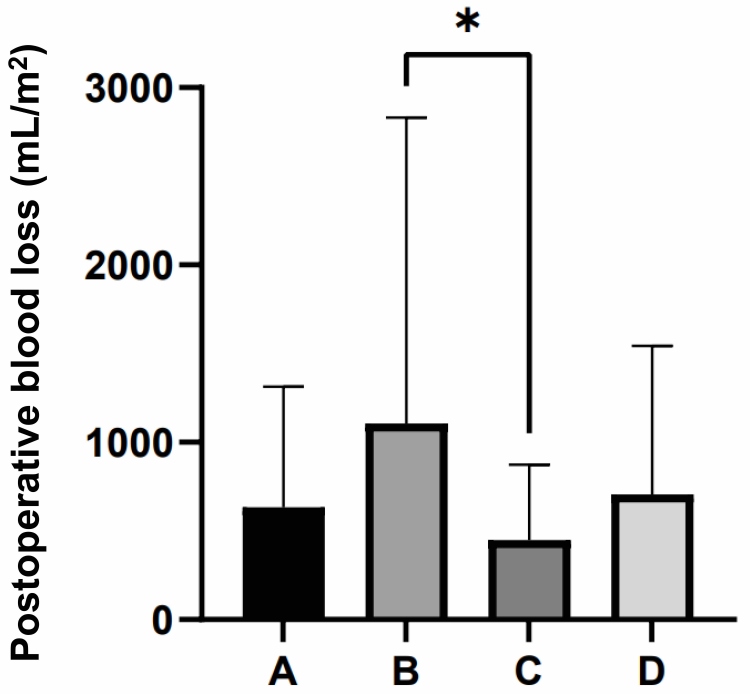

FIGURE 4. Postoperative blood loss in Groups A, B, C, and D. Bleeding volume was corrected for body surface area. The data represented as the mean ± standard deviation. Statistical analyses were performed with one-way ANOVA with Bonferroni's test as *post hoc*.

is difficult to discuss coagulation abnormalities alone because perioperative blood loss is greatly influenced by surgical bleeding. Lastly, fibrinogen levels in whole blood were assessed using the dry hematology method, which has been proven to be equivalent to the antigen and Clauss method [19].

5. Conclusions

CFF-A10 predicted fibrinogen reduction with the same accuracy as the conventional CFF-MA parameter. Faster test results with CFF-A10 would allow us for more rapid patient coagulation management and optimal blood product utilization. Sufficient fibrinogen levels but low CFF-A10 levels could be associated with coagulopathy, which can induce more postoperative blood loss. This discrepancy between CFF-A10 and fibrinogen concentrations was observed in children, especially in those with cyanotic heart disease, in our study. Further large-scale studies, particularly those specific to patients with cyanotic heart disease, are required.

ABBREVIATIONS

CFF, citrated functional fibrinogen; CK, citrated kaolin activated intrinsic pathway assay; CKH, citrated kaolin activated intrinsic pathway assay with heparinase; CRT, citrated rapid TEG assay; R time, reaction time; MA, maximum amplitude; A10, clot amplitude at 10 min; ROTEM, rotational thromboelastometry; CPB, cardiopulmonary bypass; ICU, intensive care unit; ACT, activated clotting time; ROC, receiver operating characteristic.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

MF and HI—designed the research study. MF, HI, SS and DH—performed experiments. MY—provided help and advice regarding this study and the manuscript. MF, HI and SS—analyzed the data. MF and HI—wrote the manuscript. All authors contributed to the editorial changes in the manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Ethical Review Board for Clinical Research of our hospital (R-2020199). Informed consent was not required for this retrospective observational study.

ACKNOWLEDGMENT

We would like to thank Editage (www.editage.com) for the English language editing.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1686284628143292416/attachment/Supplementary%20material.docx.

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How to cite this article: Minako Furuta, Hisakatsu Ito, Shota Sakai, Daisuke Hibi, Mitsuaki Yamazaki. Evaluation of fibrinogen function by CFF-A10 in cardiac surgery. Signa Vitae. 2023; 19(6): 52-59. doi: 10.22514/sv.2023.072.